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. >7 days (70%)
  - Increased rate of MRSA/GNR
- Increased mortality in infected patients
  - ICU: infected (25%) vs. non-infected (11%; P<0.001)
  - Hospital: infected (33%) vs. non-infected (15%; P<0.001)

MRSA, methicillin-resistant Staphylococcus aureus; GNR, gram-negative rod.
Burden of Hospital-Acquired Infections

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

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


HAIs and the Media

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

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>CLABSI (%)</th>
<th>CAUTI (%)</th>
<th>VAP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>9.9</td>
<td>2.2</td>
<td>24.4</td>
</tr>
<tr>
<td>MRSA*</td>
<td>56.6</td>
<td>60.2</td>
<td>54.4</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>16.0</td>
<td>14.9</td>
<td>1.3</td>
</tr>
<tr>
<td>VRE*</td>
<td>36.4</td>
<td>29.1</td>
<td>32.8</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>3.1</td>
<td>10.0</td>
<td>16.3</td>
</tr>
<tr>
<td>IMI or MERO-R*</td>
<td>30.5</td>
<td>33.8</td>
<td>27.8</td>
</tr>
<tr>
<td>CTX or CTZ-R</td>
<td>23.0</td>
<td>25.1</td>
<td>26.4</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>4.9</td>
<td>7.2</td>
<td>7.5</td>
</tr>
<tr>
<td>A. baumannii</td>
<td>2.2</td>
<td>1.2</td>
<td>8.4</td>
</tr>
</tbody>
</table>

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.

Cost of Antimicrobial-Resistant Infections

<table>
<thead>
<tr>
<th>Antimicrobial-resistant infection</th>
<th>188 (13.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attributable medical costs (per patient)</td>
<td>$18,588 - $29,069</td>
</tr>
<tr>
<td>Excess hospital duration</td>
<td>6.4 – 12.7 days</td>
</tr>
<tr>
<td>Societal costs (total)</td>
<td>$10.7 - $15.0 million</td>
</tr>
<tr>
<td>Attributable mortality</td>
<td>6.5%</td>
</tr>
</tbody>
</table>

1391 high-risk inpatients (Chicago teaching hospital)


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.

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

IDSA Call-to-Action

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

As resistance increases . . . number of new antimicrobials diminishes

![Graph showing decrease in number of new antimicrobials](image)

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?


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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Chief, Infectious Disease Service
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Increased Use of Antimicrobials


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

Increased antimicrobial use provides selective pressure for resistance!
MRSA

HA- and CA-MRSA Infection: Epidemiology

Vancomycin Use Continues to Increase


- Vancomycin use increased 43%
  - Likely due to increased number HA-MRSA and CA-MRSA cases that encourage greater use of vancomycin for empiric treatment
Emerging Resistance Issues: Vancomycin MIC Creep

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


Vancomycin “MIC Creep”: The Counter-Argument


Broth microdilution method with precise incremental dilutions


 Higher Vancomycin MICs Correspond to Poorer Response

Vancomycin MIC Interpretive Criteria for *S. aureus*

<table>
<thead>
<tr>
<th>Old Breakpoints</th>
<th>New Breakpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible: ≤4 µg/mL</td>
<td>Susceptible: ≤2 µg/mL</td>
</tr>
<tr>
<td>Intermediate: 8-16 µg/mL</td>
<td>Intermediate: 4-8 µg/mL</td>
</tr>
<tr>
<td>Resistant: ≥32 µg/mL</td>
<td>Resistant: ≥16 µg/mL</td>
</tr>
</tbody>
</table>


*S. aureus* Bacteremia: Hospital Costs

![Graph showing cost comparison between MRSA and MSSA in Detroit and Boston](image)


ESBL/KPC-producing Enterobacteriaceae
Evolution of β-Lactamases

Wild-Type
Penicillins
β-lactamase (TEM-1, TEM-2, SHV-1)
β-lactam/β-lactamase inhibitors; Cephalosporins
AmpC; ESBL (TEM, SHV, CTX-M)
Carbapenemase
Carbapenemase (KPC, MBL)

ESBL, extended-spectrum β-lactamase; KPC, Klebsiella pneumoniae carbapenemase; MBL, metallo-β-lactamase; TEM-1,TEM-2, SHV-1, SHV, S emulate β-lactamases.

KPC Enzymes in US: Growing Threat*

*KPC-producing Enterobacteriaceae are also known as carbapenemase-producing Enterobacteriaceae (CPE).

ESBL/KPC-producers and Clinical Outcomes

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

![Graph showing ESBL susceptibility]

TIG, tigecycline; AMK, amikacin; INH, imipenem; PTZ, piperacillin-tazobactam; MIN, minocycline; CFP, cefepime; CRO, ceftazidime; CTX, ceftriaxone; AMCL, amoxicillin-clavulanate; AMP, ampicillin.


**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*

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>KP1</th>
<th>EC1</th>
<th>KP2</th>
<th>EC2</th>
<th>SM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ertapenem</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td></td>
</tr>
<tr>
<td>Meropenem</td>
<td>&gt;32</td>
<td>2.5</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>&gt;32</td>
<td>0.5</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td></td>
</tr>
<tr>
<td>Doripenem</td>
<td>&gt;32</td>
<td>1.5</td>
<td>&gt;32</td>
<td>&gt;32</td>
<td></td>
</tr>
</tbody>
</table>

KPC-3 gene + + + +


**P. aeruginosa/Acinetobacter spp.**

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Pathogens Associated with Inadequate VAP Treatment

- PA, *P. aeruginosa*
- SA, *S. aureus*
- AS, Acinetobacter spp.
- KP, *K. pneumoniae*
- ES, Enterobacter spp.
- SP, *S. pneumoniae*


Increasing Drug Resistance

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


Carbapenem Resistance in *A. baumannii*:
Worldwide Incidence

Data from the MYSTIC study, 2004.

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.


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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University of Rochester Medical Center
Rochester, New York
Managing MRSA Infections

Managing MRSA Infections
Treatment Options

<table>
<thead>
<tr>
<th>Older</th>
<th>Newer</th>
<th>Under Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>Linezolid</td>
<td>Oritavancin</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Daptomycin</td>
<td>Iclaprim</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Tigecycline</td>
<td>Ceftobiprole</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Telavancin</td>
<td>Ceftaroline</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Low Dose (Troughs&lt;15 µg/mL)</th>
<th>Mean Trough</th>
<th>Mean AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.4 ± 3.2*</td>
<td>318 ± 111*</td>
<td></td>
</tr>
<tr>
<td>High Dose (Troughs≥15 µg/mL)</td>
<td>20.4 ± 3.2*</td>
<td>418 ± 152*</td>
</tr>
</tbody>
</table>

*P<.001.


Probability of AUC/MIC>400

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>Probability of AUC/MIC&gt;400</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>100</td>
</tr>
<tr>
<td>0.5</td>
<td>75</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

P<.0402

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.

<table>
<thead>
<tr>
<th>Low Group</th>
<th>High Group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 39)</td>
<td>(n = 16)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>5%</td>
<td>19%</td>
</tr>
<tr>
<td>Nephrotoxicity*</td>
<td>10%</td>
<td>31%</td>
</tr>
</tbody>
</table>

*Defined as rise in SCr ≥ 0.5 mg/dL.

- Clinical success and LOS were not significantly different between groups.

- Other studies have also associated higher vancomycin dosing with an increased risk of nephrotoxicity.


Skin and Skin-structure Infection (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.

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

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

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

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

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

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

**Carbapenems**
- Preferred agents (almost uniform in vitro susceptibility)
- Extensive clinical experience
- Resistance in ESBL-producing bacteria
- Some gentamicin S are R to tobramycin/amikacin

**Aminoglycosides and fluoroquinolones**
- Higher likelihood of resistance with ESBL-producing Enterobacteriaceae
- Higher likelihood of resistance with ESBL-producing Enterobacteriaceae
- Rare, though multiple mechanisms identified

**Tigecycline**
- Limited clinical data
- Limited urinary penetration

**ESBL-producing K. pneumoniae Bacteremia: Treatment**

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

86 episodes


**Infections by KPC-producing Bacteria: Treatment Options**

**Tigecycline**
- Not active against *P. aeruginosa*
- Limited clinical data
- Serum concentrations, Aes

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

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

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


## 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

Combination Antibiogram

University of Chicago Medical Center

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Monotherapy</th>
<th>Gentamicin</th>
<th>Ciprofloxacin</th>
<th>Tobramycin</th>
<th>Amikacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>All isolates (n=5064)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>84.0</td>
<td>91.0</td>
<td>86.1</td>
<td>93.4</td>
<td>95.0</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>71.5</td>
<td>88.5</td>
<td>82.9</td>
<td>88.5</td>
<td>94.2</td>
</tr>
<tr>
<td>Pip-tazo</td>
<td>74.5</td>
<td>87.4</td>
<td>84.2</td>
<td>89.2</td>
<td>90.2</td>
</tr>
<tr>
<td>P. aeruginosa (n=2115)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>66.2</td>
<td>82.3</td>
<td>75.7</td>
<td>87.8</td>
<td>91.4</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>70.3</td>
<td>87.9</td>
<td>82.0</td>
<td>93.2</td>
<td>95.0</td>
</tr>
<tr>
<td>Pip-tazo</td>
<td>74.7</td>
<td>85.5</td>
<td>82.1</td>
<td>89.6</td>
<td>92.4</td>
</tr>
<tr>
<td>A. baumannii (n=281)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>69.6</td>
<td>71.5</td>
<td>69.8</td>
<td>74.4</td>
<td>75.4</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>25.6</td>
<td>35.1</td>
<td>29.5</td>
<td>46.1</td>
<td>62.8</td>
</tr>
<tr>
<td>Pip-tazo</td>
<td>19.9</td>
<td>32.7</td>
<td>26.7</td>
<td>45.9</td>
<td>60.1</td>
</tr>
</tbody>
</table>

Pip-tazo, piperacillin-tazobactam.

Optimizing β-lactam Therapy: Maximizing %Time>MIC

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

![Graph](https://via.placeholder.com/150)

CONCENTRATION (mg/L)

Time Since Start of Infusion (h)

OPTAMA: US 2006

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

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Resistant</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime</td>
<td>2 patients (31%)</td>
<td>120 (100%)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>2 patients (14%)</td>
<td>120 (100%)</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>2 patients (31%)</td>
<td>120 (100%)</td>
</tr>
</tbody>
</table>

**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

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

- Doripenem
- Imipenem

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**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

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**Doripenem vs. A. baumannii**

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MIC ≤ 16 µg/mL</th>
<th>MIC ≥ 32 µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbiological Eradication</td>
<td>7/7 (100%)</td>
<td>4/7 (57%)</td>
</tr>
<tr>
<td>Clinical Success</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIC ≤ 16 µg/mL</td>
<td>5/7 (71%)</td>
<td></td>
</tr>
<tr>
<td>MIC ≥ 32 µg/mL</td>
<td>4/7 (57%)</td>
<td></td>
</tr>
</tbody>
</table>


**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)

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


**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