Antimicrobial Stewardship: Opportunities & Challenges In the Era of Increasing Resistance

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Disclosures

• I am a consultant or member of the speakers bureau for AstraZeneca, Cerexa, Cubist, Forest, Merck, Optimer, Pfizer, Tetraphase and Trius.
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Improving the Probability of Positive Outcomes

• Assessing Host Compromise:
  – Chronologic versus physiologic age
  – Presence of co-morbidities (i.e., malnutrition, DM, renal / hepatic Dx
  – Concomitant disease entities (i.e., HIV, transplant, rheumatologic)
  – Medical and / or surgical interventions (i.e., Blood products, medicines, recent surgery, intubation)

• Alterations in Drug Handling:
  – Hyper dynamic clearance, Volume of Distribution, Renal Dx (i.e., CRRT)
Improving the Probability of Positive Outcomes

HOST

• Organisms of Concern:
  - Staphylococcus aureus
  - Enterococci
  - Enterobacteriaceae
  - Pseudomonas
  - Acinetobacter

Epidemiology of Infection

Historic

Now

• Skin and Skin Structure
  - S. aureus
  - Streptococcus sp.
  - MRSA

• CAP
  - S. pneumoniae
  - H. influenzae
  - Atypicals
  - PRSP, MacR, TelR
  - β-lactamase producing

• HAP / VAP
  - S. aureus
  - P. aeruginosa /A. baumannii
  - Enterobacteriaceae
  - MRSA, VISA, VRSA
  - MDR, XDR
  - ESBL, CRE

• Urinary Tract Infection
  - Enterobacteriaceae
  - Enterococcus sp.
  - ESBL, CRE
  - VRE

MRSA in the Hospital & Community

• Close to 60% of S. aureus isolates from hospitalized patients are methicillin-resistant.¹

• MRSA is isolated from 59% of patients with community-acquired skin and skin structure infections.²

Characteristics of Infections due to ESBL-producing Bacteria

**Risk Factors**

**Community-onset**
- Repeat UTIs with underlying renal pathology
- Previous antibiotics (cephalosporins, fluoroquinolones)
- Previous hospitalization
- Nursing-home residents
- Older men and women
- Diabetes mellitus
- Underlying liver pathology

**Hospital-onset**
- Longer length of hospital stay
- Severity of illness (more severe, the higher the risk)
- Longer time in the ICUs
- Intubations and mechanical ventilation
- Urinary or arterial catheterization
- Previous exposure to antibiotics (cephalosporins, FQ)

**Improving the Probability of Positive Outcomes**

**IMPROVING THE ODDS**

**HOST**

**BUG**

- Frequently Utilized:
  - Vancomycin, Linezolid, Daptomycin
  - Fluoroquinolones
  - Aminoglycosides
  - B-lactams (i.e., penicillins, cephalosporins, carbapenems)

**DRUG**

**Changing Landscape for Numbers of Approved Antibacterial Agents**

Bars represent number of new antimicrobial agents approved by the FDA during the period listed.


Antimicrobial Stewardship: Part of the Solution?

Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship

The Primary Goal of Antimicrobial Stewardship: “Optimize clinical outcomes while minimizing unintended consequences of antimicrobial use”

Antimicrobial Stewardship: Consideration Across the Continuum of Care

- Hospital Setting
- Community Setting
  - “The Other Community”
    - Transitions of Care: Increased introduction of resistant organisms from the nursing home / rehabilitation facilities
  - Non-institutionalized “The True Community”
    - Increased introduction of resistant organisms from the community “home” setting

Antimicrobial Stewardship Team: Hospital Setting
Multidisciplinary Team Approach to Optimizing Clinical Outcomes

ASP = Antimicrobial Stewardship Program, ID = infectious disease, P&T = Pharmacy and Therapeutics.
Antimicrobial Expertise vs. Prescribing Volume

Unnecessary Use of Antimicrobials in Hospitalized Patients
- Prospective observational study in ICU
- 516 of 1941 days (30%) of antimicrobial therapy deemed unnecessary

Most Common Reasons for Unnecessary Days of Therapy

Appropriate Antimicrobial Therapy
- Matches antibiotic susceptibilities of the organism to the antibiotic used

“S” = Success

Improved Outcomes = Reductions in:
- Hospital and infection-related mortality
- Infection-related morbidity
- Length of hospital stay
- Days of antimicrobial therapy
- Cost of hospitalization
Inappropriate Therapy Often Due to Antibiotic Resistance

- Inappropriate therapy more likely if antibiotic resistance is present
- Antibiotic-resistant organisms are more commonly associated with inappropriate therapy

![Bar graph showing inappropriate treatment (%) for different organisms]


Appropriate Antimicrobial Therapy
An Increasing Challenge

- Impact of previous ABX therapy on outcomes of Gram-negative sepsis
  - ABX therapy in previous 90 days, patients = 310
  - Organisms
    - E. coli 31%
    - Klebsiella pneumoniae 23%
    - Pseudomonas aeruginosa 18%
  - ABX use: Cefepime > Cipro > imipenem
  - Patients with prior ABX higher RESISTANCE to cefepime, Pip/tazo, carbapenems, Cipro & gentamicin
  - Patients with prior ABX higher INAPPROPRIATE THERAPY and MORTALITY compared with patients without ABX exposure


Not Just Appropriate Therapy: RAPID Therapy in Septic Shock

- 2154 patients with septic shock
- 78.9% got effective antimicrobial therapy

![Graph showing delay in treatment (hours) from hypotension onset to effective antimicrobial therapy]

Each hour of delay carries 7.6% reduction in survival

Carbapenem Usage Continues to Rise Dramatically in the US (2003-2008)


Mortality Associated with Appropriate Therapy in Patients with Serious Infections

- Why do we see continued Mortality?
  - Continuation of terminal process
  - Delay in the initiation of therapy
  - Inadequate dose / exposure

- Pharmacodynamic goal (i.e., optimal exposure) not achieved in 16/19 (84%)
- 8/16 (50%): organism resistant to empiric therapy
- 8/16 (50%): organism susceptible but therapy not optimal
  - 6/8 organisms had MIC's at the breakpoint
  - 2/8 organisms had MIC's 1 dilution below the breakpoint

Assessment of In Vitro Potency
MIC Breakpoints

S = Susceptible
I = Intermediate
R = Resistant

Low ≤ MIC (µg/mL) ≤ High

Outcomes of Bacteremia Due to P. aeruginosa Based on the Susceptibility of Piperacillin/Tazobactam

All = Susceptible

28-Day Mortality Rate (%) in Gram-Negatives

Failure of Current Cefepime Breakpoints to Predict Clinical Outcomes in Gram-Negatives

28-Day Mortality Rate (%)
Fluoroquinolone Pharmacodynamics

• What’s the problem?
  – What’s your % of FQ-R PSA?
  – What’s your % of FQ-R E. coli?
  – When original studies done, vast majority of organism MICs ≤ 0.5 µg/ml
  
  » Now majority of susceptible isolates just below the breakpoint
  » Conventional FQ doses don’t optimize PD profile for many TARGET Gram Negative pathogens
    • Poor microbiologic eradication → promotes resistance
    • Collateral Damage → MRSA, Clostridium difficile

Should we NOT Use Quinolones for a First ICU Infection?

• 239 ICU patients with no prior antibiotic exposure
  – Screen for MDR pathogens on admit
• Multivariate analysis of risks for acquiring MDR pathogens
  – 77 patients with ICU acquired MDR organisms (55 were infection)
    » Multivariate risks for MDR acquisition: FQ use (OR 1.3), duration antibiotics (OR 1.5)
  – 135 got a quinolone (ofloxacin or ciprofloxacin), case-control matching for 72 of 135 Rx with FQ
    » Cases with more antibiotics/patient, more BL/BLI use, more aminoglycoside use
    » Cases with more ICU-acquired MRSA (26% vs 12%, p=0.015), ICU-acquired ESBL (11% vs. 1%, p=0.017) than controls
  – Maybe reserve quinolones for a second course of ICU infection

Stewardship: Supplemental Strategies

• Education is essential for any program
• Guidelines and clinical pathways can improve antimicrobial utilization
• Combination therapy – insufficient data to recommend routine use...to prevent resistance
• Streamlining or de-escalation – can decrease antimicrobial exposure and save costs
  
  » Dose optimization – an important part of stewardship
• IV-to-PO switch – can decrease LOS and health care costs


LOS = Length of stay
Optimizing Antimicrobial Exposures: Pharmacodynamics

• Considerations:
  – *In vitro* potency
  – *In vivo* exposure: pharmacokinetics
    » High drug clearance (young trauma patient)
    » Increased volume of distribution (sepsis / septic shock)
  – *In vivo* killing profile: pharmacodynamics

• Pharmacodynamic Dosing Interventions:
  – Escalated dosing: vancomycin, daptomycin
  – Once-daily aminoglycosides
  – Prolonged or continuous infusion of β-lactams

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### Once-daily vs. Conventional Three-times Daily Aminoglycoside Regimens

<table>
<thead>
<tr>
<th>Concentration (mg/L)</th>
<th>Time (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
</tr>
</tbody>
</table>

Once-daily regimen

Conventional (three-times daily regimen)

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### Strategies to Improve Efficacy and Limit Resistance for β-Lactams

Increase duration of infusion

*Continuous infusion*

– Administer loading dose, then use pump to give total daily dose IV over 24 hr period

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Treatment of Bla\textsubscript{KPC-2}-Positive *Klebsiella pneumoniae* Blood Stream Infection With Continuous Infusion Meropenem

58 yo hospitalized for aortic dissection complicated by intra-abdominal catastrophe and acute kidney injury developed bacteremia
- MDR KPC (MICs: AMK 16, TAZ ≥ 64, P/T ≥ 128, Tige ≥ 8, PMX B 32, Mbl 9)
- Cl cr -45 ml/min
- Meropenem 2 g q8 by continuous infusion

- Meropenem serum concentrations 22 mcg/mL (range 20-29)
- 6 wks of the therapy
- Microbiologic and clinical cure


Optimizing β-lactam Therapy: Maximizing Percent T>MIC

Increased duration of infusion

<table>
<thead>
<tr>
<th>Time Since Start of Infusion (h)</th>
<th>MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

Concentration (mg/L)

- Same dose and dosing interval, 100-250ml, however, change duration of infusion (0.5 hr → 3-4hr)

Intravenous Antibiotic Pharmacodynamics against *Pseudomonas aeruginosa* from TRUST 12 - Benefits of Prolonged Infusion

<table>
<thead>
<tr>
<th>1,533 <em>P. aeruginosa</em> from 56 US hospitals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotic</strong></td>
</tr>
<tr>
<td>Cefepime</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Doripenem</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
</tr>
<tr>
<td>Meropenem</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Pip/tazo</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Cumulative Fraction of Response in Pediatric Patients with Pseudomonas

<table>
<thead>
<tr>
<th>LOW Dose Regimen</th>
<th>Infusion Duration</th>
<th>% S</th>
<th>CFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime 30 q8h</td>
<td>0.5 h</td>
<td>95</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>3.0 h</td>
<td>95</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>Continuous</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Piperacillin</td>
<td>0.5 h</td>
<td>95</td>
<td>54</td>
</tr>
<tr>
<td>Tazobactam 75 Q6h</td>
<td>3.0 h</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>Meropenem 20 q8h</td>
<td>0.5 h</td>
<td>98</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>3.0 h</td>
<td>98</td>
<td></td>
</tr>
</tbody>
</table>

Doses in mg/kg per dose. Bactericidal exposures = 40% for carbapenems; 50% for other β-lactams


Pneumonia: The Continuum of Pulmonary Disease

- Community-acquire (CAP)
- Healthcare-associated (HCA)- is a relatively new clinical entity that includes a spectrum of adult patients who have a close association with acute care hospitals or reside in chronic care settings that increase their risk for pneumonia caused by multidrug-resistant pathogens.
- Hospital-acquired / Ventilator Associated (HAP / VAP)

Frequency of Pathogens between VAP and HAP

<table>
<thead>
<tr>
<th>Pathogen, by class</th>
<th>No. (%) of Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICU (n=105)</td>
</tr>
<tr>
<td>Gram-positive cocci</td>
<td></td>
</tr>
<tr>
<td>MSSA</td>
<td>11 (2.5)</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>48 (10.9)</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td></td>
</tr>
<tr>
<td>E. coli</td>
<td>10 (2.7)</td>
</tr>
<tr>
<td>K. pneumonia</td>
<td>6 (1.6)</td>
</tr>
<tr>
<td>A. baumannii</td>
<td>5 (1.4)</td>
</tr>
<tr>
<td>Acinetobacter</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>40 (9.6)</td>
</tr>
<tr>
<td>Other</td>
<td>32 (8.0)</td>
</tr>
</tbody>
</table>

Single Center, UNC, Period 2000 through 2003, infection control surveillance. Specimens isolated by BAL, expectorated sputum, or tracheal aspirate.

Start Broad, Then Streamline Therapy

Infected Patient
Site(s) of Infection
Community vs. Hospital Infection
Laboratory Tests
Collection of Infected Materials:
Gram Stain
Culture Results
Identification of organism
Sensitivity
Abx

Antimicrobial Spectrum of Activity
Baseline

1 h
24-48 h
48-72 h
72-96 h

Discontinue agents
Streamline therapy
Precision & Time

Hartford Hospital:
VAP Pathway – EMPIRIC Therapy

1st Line Regimen:
Dosage
(1st Line
50ml/min)
Adjustment for Renal Dysfunction
(Vancomycin, 30 - 49 < 30 CRRT
≥ 50ml/min)
l
Tobramycin
plus
High Dose β-lactam
plus

Medical Intensive Care Unit
Surgical and Neurosurgical Intensive Care Unit
Cefepime
Piperacillin / Tazobactam
2g q 8 hr
(3 hr infusion
Continuous Infusion)
2g q 8 hr
(3 hr infusion
Continuous Infusion)
18g Continuous Infusion
Meropenem
Vancomycin
(Tobramycin)
plus

CI = continuous infusion; CRRT = continuous renal replacement therapy

• Target entire MIC distribution
  • Focus on 4, 8 A/16 µg/ml
  • Anticipate variable PK → Cl & Vd
  • Target PD profile → 50% fT>MIC

Improved Outcomes: VAP Pathway

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Historic</th>
<th>Pathway</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAT=Appropriate Antibiotic Therapy</td>
<td>53 (71.6)</td>
<td>29 (28.7)</td>
<td>0.007</td>
</tr>
<tr>
<td>LOS=Length of Stay</td>
<td>11.7 ±± ±±</td>
<td>8.1  &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>IR=Infection Related</td>
<td>20.1 0.113</td>
<td>15 (16.0) 0.007</td>
<td></td>
</tr>
<tr>
<td>MDR=Multi-Drug Resistant</td>
<td>9 (9.6) 0.006</td>
<td>8 (8.5) 0.029</td>
<td></td>
</tr>
<tr>
<td>Outcome Historic n = 74</td>
<td>Days to AA T (mean ±± ±± SD)</td>
<td>1.7 ±± ±±</td>
<td>2.6</td>
</tr>
<tr>
<td>AA T within 24 hrs</td>
<td>36 (48.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOS (mean ±± ±± SD)</td>
<td>26.1 ±± ±±</td>
<td>18.5</td>
<td></td>
</tr>
<tr>
<td>IR</td>
<td>31.9 ±± ±±</td>
<td>19.9</td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>43.3 ±± ±±</td>
<td>23.6</td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superinfection</td>
<td>26 (35.1)</td>
<td>20 (27.0)</td>
<td>0.282</td>
</tr>
<tr>
<td>MDR-Superinfection</td>
<td>24 (32.4)</td>
<td>20 (27.0)</td>
<td>0.113</td>
</tr>
<tr>
<td>All Cause Mortality</td>
<td>26 (35.1)</td>
<td>15 (16.0) 0.007</td>
<td></td>
</tr>
<tr>
<td>IR-Mortality</td>
<td>16 (21.6) 0.007</td>
<td>15 (16.0) 0.007</td>
<td></td>
</tr>
</tbody>
</table>

The Pathway Statistically Decreased:
Infection Related Mortality
Infection Related Length of Stay
Time to Appropriate Therapy
Number of Super-infections

De-escalation of Antibiotic Therapy

- Approach to de-escalation / streamlining
  - Initial treatment with broad-spectrum antibiotics to cover most probable pathogens\(^1,2\)
  - Discontinue antibiotic therapy if no evidence of infection (bronchoalveolar lavage samples negative)\(^3\)
  - Narrow the spectrum of activity when possible, based on culture findings\(^1,2\)
  - Shorten course of therapy, based on culture findings and clinical course\(^4\)

- Exceptions to general approach
  - Do not discontinue antibiotics in a patient who is decompensating
  - Patients may be ill and require therapy, notwithstanding negative culture results


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Economics of the VAP Pathway

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n=73)</th>
<th>Pathway (n=93)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOTVAP (days)</td>
<td>27.1±18.5</td>
<td>12.7±8.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LOS (days)</td>
<td>35.9±23.0</td>
<td>28.9±17.3</td>
<td>0.076*</td>
</tr>
<tr>
<td>COSTVAP ($75K)</td>
<td>$75K</td>
<td>$76K</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COSTafter ($95K)</td>
<td>$95K</td>
<td>$76K</td>
<td>0.077*</td>
</tr>
</tbody>
</table>

- Treatment on Clinical Pathway was independently associated with lower total LOS after VAP (p=0.012) and lower total hospital costs after VAP (p=0.033) in multivariable models.


LOTVAP = length of VAP treatment; LOS = total length of hospital stay after identification of VAP; COSTVAP = hospital costs (2007$) of treating VAP; COSTafter = total hospital costs (2007$) of treating VAP after VAP identification; Antibiotic Cost = acquisition cost of antibiotics used to treat VAP.
What is “Collateral Damage”?  
“Collateral Damage”
- a term used to refer to ecological adverse effects of antibiotic therapy; namely, the selection of drug-resistant organisms and the unwanted development of colonization or infection with multidrug resistant organisms (i.e., Clostridium Difficile Infection)

- Two antibiotic classes commonly linked to collateral damage:
  - Cephalosporins & Fluoroquinolones


Antimicrobial Cross-Resistance Among Selected Gram-Negative Bacilli

<table>
<thead>
<tr>
<th></th>
<th>Pseudomonas aeruginosa</th>
<th>Entrobacter Species</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ciprofloxacin Resistant (n = 1945)</td>
<td>Ciprofloxacin Susceptible (n = 5299)</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>66.0</td>
<td>21.7</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>39.8</td>
<td>14.0</td>
</tr>
<tr>
<td>Imipenem</td>
<td>37.6</td>
<td>10.9</td>
</tr>
<tr>
<td>Ambicaxin</td>
<td>26.0</td>
<td>5.6</td>
</tr>
</tbody>
</table>

Data are presented as percentages of strains exhibiting cross-resistance, 1994-2000.

Carbapenems: Saving the Best for Last

- Broad spectrum of activity including Pseudomonas
  - Imipenem
  - Meropenem
  - Doripenem
- Broad spectrum but lacking Pseudomonas activity
  - Ertapenem
Ertapenem

- US experience: Sustained efficacy & safety over more than 10 years
  - Complicated urinary tract infection
  - Complicated intra-abdominal infection
  - Complicated skin & skin structure including diabetic foot infections
- Active against ESBL-producing Enterobacteriaceae organisms
  - 2005 - 2010: 261 patients with ESBL bloodstream infections
  - Outcomes equivalent between ertapenem and group 2 carbapenems (e.g., imipenem & meropenem)


What is the concern with Ertapenem?

- Alteration in Gut Flora
  - Selection of resistant Enterobacteriaceae
  - Selection of resistant Pseudomonas aeruginosa

- Alteration of Institutional Ecology
  - Selection of Group 2 carbapenem (e.g., imipenem, meropenem, doripenem) resistant Pseudomonas aeruginosa

ABC = antibacterial R in the colon

ABC study: examine effect of ertapenem on gut flora employing selective media

- Rectal swabs in all pts enrolled in two IAI studies
  - ertapenem vs piperacillin/tazobactam
  - ertapenem vs ceftriaxone / flagyl

### Resistant Gram-negative Bacilli Isolated from Rectal Swabs

<table>
<thead>
<tr>
<th>Organism</th>
<th>Ertaipenem (N=196)</th>
<th>Ceftriaxone/Metronidazole (N=193)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>DCOT</strong></td>
<td><strong>DCOT/TOC</strong></td>
</tr>
<tr>
<td>ORO-R Enteric</td>
<td>9 (4.6)</td>
<td>4 (2.1)</td>
</tr>
<tr>
<td>ETP-R Enteric</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>ESBL-Enteric</td>
<td>1 (0.5)**</td>
<td>2 (2.6)**</td>
</tr>
<tr>
<td>IPM-R Ps</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*P<0.001 for between-treatment comparison
**P<0.05 for between-treatment comparison
†P<0.001 for between-treatment comparison
‡P<0.05 for between-treatment comparison

* Emergent Ceftriaxone-resistant Enterobacteriaceae: 19 E coli, 20 Enterobacter cloacae, 10 K pneumoniae, 3 Entrobacter aerogenes, 3 Citrobacter freundii, 2 K oxytoca


### Resistant Gram-negative Bacilli Isolated from Rectal Swabs

<table>
<thead>
<tr>
<th>Organism</th>
<th>P/T-R Enteric (N=155)</th>
<th>Piperacillin-Tazobactam (N=156)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>DCOT</strong></td>
<td><strong>DCOT/TOC</strong></td>
</tr>
<tr>
<td>P/T-R Enteric</td>
<td>1 (0.6)</td>
<td>18 (11.5)**</td>
</tr>
<tr>
<td>ETP-R Enteric</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>ESBL-Enteric</td>
<td>1 (0.6)</td>
<td>4 (2.6)</td>
</tr>
<tr>
<td>IPM-R Ps</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*P<0.05 for between-treatment comparison
†P<0.001 for between-treatment comparison


Ertapenem Does NOT Adversely Effect the Hospital Ecology → *P. aeruginosa* Susceptibility to Group 2 Agents

Clinical Studies
- Crank, 44th IDSA Annual Meeting, Toronto, CA 2006. Abst. 265
- Carmeli et al., *Diagn Microbiol Infect Dis* 2011;70:367-372
- Graber et al., *Epidemiology Infection* 2012;140(1):115-25


Collateral Damage v. Collateral Benefit
Susceptibility of P. aeruginosa: 3 Years of Formulary Inclusion

Collateral Damage v. Collateral Benefit
Minimal Risk of Imipenem-Resistant P. aeruginosa with Ertapenem: 4-Year Retrospective Study: Israel
Strategies to Optimize Clinical & Microbiologic Outcomes & Slow the Development of Resistance

- Antimicrobial Stewardship Efforts
  - Appropriate Initial Therapy
    - Right DRUG(s)
    - Optimize Exposures (PD profile)
  - De-escalation / Streamlining
    - <50% of nosocomial sepsis cases b/c susceptibility & previous ABX [Heeren et al., CCM 2012;40(5):1404-9]
  - Reduce Duration of Therapy

Unintended Consequences of Poor Antimicrobial Practices

- Development of resistance in the target pathogen
- Development of superinfection @ original infection site
- Development of new infection (i.e., *Clostridium difficile*)
- Increased cost of care

Societal and Hospital Costs of Antimicrobial-Resistant Infections

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Patients with ARI</th>
<th>Patients without ARI</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>1391</td>
<td>168 (13.5)</td>
<td>1203 (86.5)</td>
</tr>
<tr>
<td>APACHE III Score*</td>
<td>42.1</td>
<td>54.8</td>
<td>40.1</td>
</tr>
<tr>
<td>Duration of Stay* (days)</td>
<td>10.2</td>
<td>24.2</td>
<td>8.0</td>
</tr>
<tr>
<td>HAI* (n)</td>
<td>260</td>
<td>130</td>
<td>125</td>
</tr>
<tr>
<td>Cost per Day* (US$)</td>
<td>1691</td>
<td>2498</td>
<td>1581</td>
</tr>
<tr>
<td>Total Cost* (US$)</td>
<td>$15,207</td>
<td>$58,029</td>
<td>$13,210</td>
</tr>
<tr>
<td>Death* [n (%)]</td>
<td>70</td>
<td>34 (18.1)</td>
<td>36 (18.0)</td>
</tr>
</tbody>
</table>

* P<0.001. Mean value shown in table. APACHE=Acute Physiology and Chronic Health Evaluation; ARI=antimicrobial-resistant infections; HAI=healthcare-acquired infection. 

Hospital and Societal Costs of Antimicrobial-Resistant Infections

<table>
<thead>
<tr>
<th>Organism</th>
<th>Mean Cost Per Patient Healthcare-acquired ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin Resistant Enterococci</td>
<td>$66,416</td>
</tr>
<tr>
<td>Methicillin Resistant Staphylococcus aureus</td>
<td>$46,236</td>
</tr>
<tr>
<td>Acinetobacter resistant to antimicrobics</td>
<td>$97,444</td>
</tr>
<tr>
<td>Klebsiella or E. coli resistant to quinolones or</td>
<td>$26,549</td>
</tr>
<tr>
<td>Third generation cephalosporins</td>
<td></td>
</tr>
<tr>
<td>Multiple ARIs</td>
<td>$157,835</td>
</tr>
</tbody>
</table>


Strategies to Optimizing Efficacy and Minimize Collateral Damage In Our Patients

- **Prevent it** –
  - Vaccination programs in the community
  - Utilization of non-antibacterial interventions (i.e., probiotics, medicines able to stimulate the body's defense against infections)
  - Strong infection control practices in the hospital

- **Respect it** –
  - Despite our efforts, infection will develop in patients in both the community & the hospital setting

- **Do Not Yield to it** –
  - Understand the likely causative pathogens and local resistance
  - Utilization of real-time, point of care molecular diagnostics
  - Make good decisions regarding the choice, dosage and duration [use of biomarkers] of antibiotic(s)
  - Understand that the MOST EXPENSIVE antibiotic is the one that does not work