Infectious Disease Issues in the Intensive Care Unit

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Overview

- Emerging antibiotic resistance
  - Gram positives: MRSA
  - Gram negatives: ESBL producers, Pseudomonas, Acinetobacter
- Empiric antibiotic therapy
- Optimizing antibiotic therapy in the ICU
- Newer therapies, in the pipeline
Case Presentation

56 year old man with diabetes, chronic kidney disease

- **11/05**: Admitted with hyperkalemia, volume overload. Developed R arm cellulitis at PIV site, 1/2 blood cx MRSA, d/c home with 10 day course of TMP/SMX.

- **1/06**: Started on hemodialysis for uremia and volume overload.

- **2/06**: Readmitted with hypotension, 2/2 blood cx MRSA, HD catheter removed. Persistent bacteremia for 10 days, negative TEE, but SVC thrombosis noted, treated with 6 wk course of IV vancomycin

- **4/06**: Develops low back pain, difficulty walking; MRI reveals L4-5 epidural abscess, osteomyelitis and discitis.
Needle biopsy of L4-5 lesion performed

That evening, had a PEA arrest, resuscitated, but pupils fixed and dilated

Supportive care withdrawn

Culture from biopsy:
- Vancomycin-intermediate S. aureus (VISA)

Molecular typing:
- USA300 clone of community-associated MRSA

Graber CJ et al Emerging Infectious Diseases 2007; 491-493
MRSA Update

- MRSA in the ICU: To screen or not to screen?
- Community-associated MRSA
- Emerging resistance: vancomycin “MIC creep”, VISA, VRSA
- Antimicrobial therapy
  - Optimizing use of vancomycin
  - Vancomycin alternatives
  - New therapies
Methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA) Among ICU Patients, 1995-2004

Source: National Nosocomial Infections Surveillance (NNIS) System
Fact, Fiction, or No Data: What Does Surveillance for Methicillin-Resistant *Staphylococcus aureus* Prevent in the Intensive Care Unit?

Aaron M. Milstone and Trish M. Perl

Departments of Pediatrics and Medicine, Division of Infectious Diseases, Johns Hopkins University School of Medicine, and Department of Hospital Epidemiology and Infection Control, The Johns Hopkins Hospital, Baltimore, Maryland

- Potential benefit: decrease incidence of MRSA infection, morbidity, and cost of care
- What’s the data?: Literature is controversial, poor-quality studies, no randomized-controlled trials
- While active surveillance enables identification of colonized patients, no clear evidence that interventions (i.e. isolation, decolonization) are effective in reducing MRSA infection rates
- “We do not believe that active surveillance cultures (ASCs) should be mandated. The decision…should be left to individual hospitals that can best assess the need for ASCs as part of a comprehensive MRSA control plan.”
CA-MRSA in the ICU

- Necrotizing pneumonia
  - Preceding influenza or “influenza-like” illness
  - Necrotizing or cavitary infiltrates
- Invasive skin and soft tissue infections
  - Necrotizing fasciitis
  - Pyomyositis
- Severe sepsis syndromes
USA300 is the most common genotype, clonal spread throughout the U.S.

In contrast to hospital-associated MRSA, generally susceptible to most antibiotics

However, resistance in CA-MRSA is emerging

- Multi-drug resistant strain of USA300: plasmid-mediated resistance to macrolides, clindamycin, and mupirocin among MSM in San Francisco & Boston
- Tetracycline resistance has been observed
- Vancomycin-intermediate CA-MRSA

Clinical MRSA blood isolates collected at a single tertiary care center

MRSA = methicillin-resistant Staphylococcus aureus; MIC = minimum inhibitory concentration.
**Relationship of MIC to Vancomycin Treatment Failures in MRSA Infections**

The graph illustrates the relationship between the minimal inhibitory concentration (MIC) of vancomycin and the failure rate of treatment for MRSA infections. The data points are as follows:
- At a MIC of 0.5 μg/mL, the failure rate is 47.6%, (10/21 pts).
- At a MIC of 1 μg/mL, the failure rate is 70.0%, (12/17 pts).
- At a MIC of 2 μg/mL, the failure rate is 92.0%, (23/25 pts).

MIC, minimal inhibitory concentration

## Vancomycin: New MIC Breakpoint

<table>
<thead>
<tr>
<th></th>
<th>OLD</th>
<th>NEW</th>
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<tbody>
<tr>
<td>Susceptible</td>
<td>$\leq 4 \ \mu g/mL$</td>
<td>$\leq 2 \ \mu g/mL$</td>
</tr>
<tr>
<td>Intermediate</td>
<td>8-16 $\mu g/mL$</td>
<td>4-8 $\mu g/mL$</td>
</tr>
<tr>
<td>Resistant</td>
<td>$\geq 32 \ \mu g/mL$</td>
<td>$\geq 16 \ \mu g/mL$</td>
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Vancomycin Intermediate-Resistant S. aureus (VISA)

- 1997: 1st case of VISA reported in Japan
- 4 cases in UCSF hospitals
- Mechanism of resistance: thickening of bacterial cell wall
Vancomycin Resistant S. aureus (VRSA)

- Since 2002, 7 cases of VRSA reported
  - 5/7 cases from Michigan
    - 6 ulcers/wounds
    - 1 nephrostomy tube urine specimen
- Common features:
  - chronic comorbidities
  - h/o MRSA and VRE infection/colonization
  - prior vancomycin exposure
- Mechanism of resistance:
  - Plasmid-mediated transfer of \textit{vanA} gene from VRE to \textit{S. aureus} in setting of polymicrobial biofilm

Sievert DM et al Clin Infect Dis 2008; 45: 668-74
Is Vancomycin Obsolete?
Optimize Use of Vancomycin

- Consider use of vancomycin loading dose 25-30 mg/kg in seriously-ill patients with suspected MRSA.

- Higher doses (15-20 mg/kg every 8-12 hours) may be needed.

- Vancomycin trough monitoring: goals 15-20 µg/mL for serious infections due to MRSA.
Ensure Appropriate and Adequate Use of Vancomycin

- **MSSA**: Vancomycin is inferior to β-lactam for treatment
  - Slower rates of in vitro bacterial killing
  - Higher mortality rates associated with use of vancomycin vs. β-lactam for treatment of MSSA bacteremia

- **MRSA bacteremia**: Minimum 2 week course of IV therapy (including catheter-related bacteremia)
  - Lower success rates among those treated with < 14 days of therapy vs. ≥ 14 days

Current FDA-Approved Drugs for the Treatment of MRSA

### Nosocomial Pneumonia
- Vancomycin (IV)
- Linezolid (IV, PO)

### Complicated Skin & Skin Structure Infections (cSSTI)
- Vancomycin (IV)
- Linezolid (IV, PO)
- Daptomycin (IV)
- Tigecycline (IV)

### Bacteremia/ R-sided endocarditis
- Vancomycin (IV)
- Daptomycin (IV)
<table>
<thead>
<tr>
<th>Disease</th>
<th>Current Data</th>
<th>Clinical Practice</th>
</tr>
</thead>
</table>
| **Nosocomial Pneumonia** | Retrospective pooled analysis of two studies ↑ cure rates & survival with linezolid vs. vancomycin | - Vanco or linezolid  
- Await results of ongoing randomized clinical trial |
|                         | Wunderink RG *Chest* 2003                                                   |                                                                                   |
| **Bacteremia/endocarditis** | Randomized controlled trial: daptomycin noninferior to vancomycin           | - Vanco or daptomycin   
- Consider Rx with higher dose daptomycin (10 mg/kg vs. 6 mg/kg) |
|                         | Fowler VG *NEJM* 2006                                                      |                                                                                   |
| **cSSTI**                | No randomized clinical trial has shown superiority of comparator to vancomycin | - Vanco, linezolid, daptomycin, or tigecycline                                    |
What’s in the Pipeline for MRSA?

**Lipoglycopeptides**
- Dalbavancin - cSSTI, CR-BSI
- Telavancin – cSSTI, nosocomial PNA, uncomplicated S. aureus bacteremia
- Oritavancin - cSSTI

**Cephalosporins**
- Ceftobiprole - cSSTI, nosocomial PNA
- Ceftaroline - cSSTI

* Ongoing or completed clinical trials
Gram Negatives

- Gram-negative pathogens are a growing challenge in the treatment of hospital-acquired infections due to increasing resistance.
- Forces the use of previously reserved antibiotic agents as empiric therapy.
- Earlier use of broad-spectrum agents may contribute to the development of subsequent resistant bacterial strains.
- Limited options for MDR organisms require treatment with potentially toxic agents.
The Role of Gram-Negative Bacilli in Nosocomial Infections

NNIS epidemiologic data of ICU infections in 2003

<table>
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<tr>
<th>Infection Type</th>
<th>Frequency (%)</th>
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<tbody>
<tr>
<td>Pneumonia episodes (n = 4365)</td>
<td>65.2</td>
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<tr>
<td>Bloodstream infections (n = 2351)</td>
<td>23.8</td>
</tr>
<tr>
<td>Urinary tract infections (n = 4109)</td>
<td>71.1</td>
</tr>
<tr>
<td>Surgical site infections (n = 2984)</td>
<td>33.8</td>
</tr>
</tbody>
</table>

NNIS = National Nosocomial Infections Surveillance System; ICU = Intensive Care Unit

Problem Pathogens

- Declining research investments in antimicrobial development

- The Antimicrobial Availability Task Force of the IDSA has identified these as problematic pathogens:

  1) Extended Spectrum β-lactamase (ESBL) producing Enterobacteriaceae
  2) *Pseudomonas aeruginosa*
  3) *Acinetobacter baumannii*
Extended Spectrum $\beta$-Lactamase (ESBL) Producing Pathogens

- Most frequently detected in *Klebsiella* spp. and *E. coli*
- Plasmid-mediated, constitutively produced, diverse group of enzymes (> 200 described)
- Confer resistance to penicillins, cephalosporins, and aztreonam
- Laboratory detection may be difficult at times
- Risk factors:
  - Prior receipt of 3rd generation cephalosporin, aztreonam, or fluoroquinolone
  - Total duration of prior antibiotic therapy
  - Prolonged hospitalization
Treatment of ESBL Infections

- **Carbapenems** are the drugs of choice for serious infections even if other antibiotics are susceptible in vitro.

![Graph showing all-cause 14 day mortality for different treatment options: Carbapenems (4%), Quinolones (36%), Other B-lactams (44%), No active abx (64%). Paterson DL et al. *C/D.* 2003;39:31-7 2003]
Carbapenems

- Stable to ESBL, AmpC and other β-lactamases
- Imipenem and meropenem
  - Active against *Pseudomonas* and *Acinetobacter* spp.
- Ertapenem
  - Not active against *Pseudomonas* and *Acinetobacter*
  - Should not select for cross-resistance to other carbapenems
  - Convenient dosing: 1 g IV q24h (CrCl > 30 ml/min)
  - Indicated for treatment of:
    - Intraabdominal infections, acute pelvic infections, CAP, complicated UTIs, complicated skin and soft tissue infections including diabetic foot, & prophylaxis in colorectal surgery
    - ATS guidelines recommend for “early-onset” VAP

Resistance to Imipenem and Ceftazidime Continues to Rise in *Pseudomonas aeruginosa*

- Independent study of 8,244 *P. aeruginosa* ICU isolates collected from 1994 to 2000 reported the following average susceptibilities:
  - Tobramycin, 87%
  - Imipenem, 83%
  - Amikacin, 90%
  - Piperacillin-tazobactam, 78%
  - Cefepime, 71%


Pseudomonas aeruginosa

- **Important ICU pathogen** (2003 NNIS surveillance):
  - 18.1% of hospital-acquired PNA
  - 16.3% of UTIs
  - 9.5% of surgical site infections

- **Increasing rates of multi-drug resistance. Risk factors:**
  - Immunocompromised state
  - Prolonged hospitalization, ICU stay
  - Use of invasive devices, mechanical ventilation
  - Prior and prolonged antibiotic use
Treatment of *Pseudomonas*

- Optimize dosing strategies when treating *Pseudomonas*
  - *higher doses*
  - *more frequent dosing*
  - *longer infusion time (continuous or prolonged infusion)*

- Time-dependent antibiotics: **maximize** $T > MIC$
  - Piperacillin/tazobactam 4.5 grams IV Q6h (CLcr > 20)
  - Cefepime 2 grams IV Q12h (CLcr > 60)
  - Imipenem 500 mg - 1 gram IV Q6h (CLcr > 50)

- Concentration-dependent antibiotics: **maximize concentration**
  - Ciprofloxacin 400 mg IV Q8h (CLcr > 50)
  - Levofloxacin 750 mg IV Q24h (CLcr > 50)
Resistance Continues to Increase in Acinetobacter spp

Data from the National Nosocomial Infections Surveillance System, ICU isolates.

**Acinetobacter**

- Important cause of ventilator-associated PNA, bloodstream infections
- Multiple mechanisms of resistance, often multi-drug resistant (> 3 classes of drugs)
- Risk factors for colonization and infection:
  - ICU stay
  - Recent surgery
  - Tracheostomy, CVC, mechanical ventilation, enteral feedings
  - Rx with 3rd generation cephalosporin, FQ, carbapenems
- Outbreaks due to contaminated respiratory therapy and ventilator equipment, cross-infection by HCWs who have cared for infected or colonized patients

Munoz-Price L. S. and Weinstein R.A. NEJM 2008; 358:1271-81
**Treatment of Acinetobacter**

- **Susceptible isolates:** broad-spectrum cephalosporins, $\beta$-lactam-$\beta$-lactamase inhibitor combination, carbapenems

- **Multi-drug resistant isolates:**
  - *Colistin:* monitor for nephrotoxicity, neurotoxicity
  - *Tigecycline:* a new glycylcycline antibiotic with activity against MDR *Acinetobacter*, but recent reports of resistance described
  - Combination therapy: in vitro synergy/ additive effects observed with colistin + imipenem, rifampin, or azithromycin

Munoz-Price L. S. and Weinstein R.A. NEJM 2008; 358:1271-81
Antibiotic resistance associated with increased mortality, length of stay and healthcare costs

**MDR P. aeruginosa**
- Mortality: 12% vs. 21%, P=0.04
- Cost: $22,116 vs. $54,081, P=0.001

**ESBL-producers in bacteremia**
- Mortality: 18% vs. 35%, P=0.01
- Cost: $16,877 vs. $46,970, P<0.001

**MDR Acinetobacter spp**
- Mortality: 17.6% vs. 26%, P=0.21
- LOS: 20 days vs. 28 days, P=0.02
The Case for Optimized Therapy: Few New Antibiotics Approved


Only 4 new antibiotics were approved between 2003-2007.
### Bad Bugs - No Drugs?

<table>
<thead>
<tr>
<th>Gram Positive</th>
<th>Gram Negative</th>
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<tbody>
<tr>
<td>Dalfopristin/quinupristin (Synercid®) – 1999</td>
<td>Ertapenem (Invanz®) – 2003</td>
</tr>
<tr>
<td>Linezolid (Zyvox®) – 2000</td>
<td>Tigecycline (Tygacil®) – 2005</td>
</tr>
<tr>
<td>Daptomycin (Cubicin®) – 2003</td>
<td>Doripenem (Doribax®) – 2007</td>
</tr>
<tr>
<td>Tigecycline (Tygacil®) – 2005</td>
<td><em>No new antibiotic classes for gram negatives on the horizon</em></td>
</tr>
</tbody>
</table>

Dalbavancin – 2009?
Telavancin – 2009-10?
Oritivancin – 2009-10?
Ceftobiprole – 2008?
Ceftaroline – 2009-10?
Optimizing Antibiotic Use in the ICU
Approach to Empiric Antibiotics

- What is the source? Lungs, urinary tract, catheter, abdomen
- Consider the host: immunocompromised, HIV, nursing home resident, etc.
- Community-acquired:
  - Exposures, travel history, other epidemiologic risk factors
- Hospital-acquired:
  - Prior antibiotic use
  - History of/ risk factors for antibiotic-resistant organisms
  - Hospital antibiogram – consider local bacteriology, susceptibility patterns
Empiric choices in patients at risk for nosocomial gram-negatives

- **Cefepime**
  - Pros: good pseudomonas activity
  - Cons: not reliable for ESBLs, ↑ resistance in enterobacter

- **Piperacillin-tazobactam**
  - Pros: good pseudomonas activity
  - Cons: not reliable for ESBLs and enterobacter

- **Quinolones**
  - Pros: none
  - Cons: high levels of resistance in all nosocomial pathogens

- **Aminoglycosides**
  - Pros: most reliably active versus nosocomial pathogens
  - Cons: inferior as a single agent, toxicities

- **Imipenem/Meropenem**
  - Pros: reliable activity against all enterobacteriaceae (ESBL, AmpC)
  - Cons: may select for carbapenem resistant pseudomonas
**De-escalation Algorithm**

- **Rapid initiation of empiric broad antibiotic therapy**
- **Narrow antibiotics based on microbiology data**
- **Clinical response should guide need for further work-up, antibiotic duration**

Adapted from Kollef MH. *Drugs.* 2003;63:2157-2168.
Treat for the shortest effective duration

- Chastre et al 2003: 8 days vs. 15 days for VAP
  - No mortality difference
  - Patients on shorter course therapy had more relapses (40.6% vs. 25.4%) with non-lactose fermenters but recurred with fewer resistant organisms
- 1 week course for treatment of VAP, consider longer courses for:
  - *Pseudomonas, Acinetobacter, Stenotrophomonas*
  - MRSA

Chastre et al. *JAMA* 2003; 290 2588-98
Empiric combination therapy for gram-negative pathogens may be warranted given local resistance rates however…..

Once the pathogen and susceptibilities are known, there is no evidence that combination therapy is beneficial in gram-negative sepsis or pneumonia.

Beta-lactam plus an aminoglycoside or a fluoroquinolone vs. beta-lactam monotherapy

- No mortality benefit for combination therapy
- Combination therapy does not prevent or delay the emergence of resistance while on therapy

Consider only in high risk patients:

- Neutropenics
- Documented serious or MDR pseudomonal infections (pneumonia, meningitis, endocarditis)

Bochud P Crit Care Med 2004;32:S495-512; Paul M Cochrane Database of Systematic Reviews 2006
Antibiotic Treatment in the ICU

A Balancing Act

Appropriate Initial Antibiotic Treatment

Avoid Unnecessary Antibiotics
MRSA is evolving: community MRSA, emerging vancomycin resistance

Antimicrobial resistance against gram negatives is increasing

While there are new drugs in development for MRSA, no new antibiotic classes against gram negatives are on the horizon

Practice appropriate initial empiric therapy and de-escalation once culture and susceptibility and other clinical data become available

Optimize antibiotic dosing and use short course therapy when appropriate