Updates on the Management of Hospital Acquired Infections and Resistant Organisms

Kaitlin McGinn, PharmD
Assistant Clinical Professor, Critical Care
Auburn University, Harrison School of Pharmacy
November 8th, 2015

Conflict of Interest

I, Kaitlin McGinn, have no actual or potential conflict of interest in relation to this program.

Objectives

1. Discuss emerging resistant organisms and their mechanism of resistance
2. Develop treatment strategies for resistant organisms and hospital acquired infections
3. Identify areas for future research in optimizing therapy for resistant pathogens
Healthcare Associated Infections

- Affects 1 in 25 hospitalized patients
- Causes
  - In hospital transmission
  - Excessive antibiotic use
  - Up to 50% of inpatient antibiotic use is inappropriate

Clinical Infectious Disease. 2007;44:159-77.

Healthcare Associated Infections

- Resistant organisms cause the majority of infections
  - ~2 million patients/year in the US develop a resistant infection
- "No ESKAPE" or updated to “ESCAPE”

- Enterococcus faecium
- Staphylococcus aureus
- Clostridium difficile
- Acinetobacter baumannii
- Pseudomonas aeruginosa
- Enterobacteriaceae (includes Enterobacter species, Klebsiella pneumonia, Escherichia coli, and other pathogens)


Defining Resistance

- Multidrug-resistant (MDR)
  - Resistant to at 3 drug classes OR
  - Resistant to 1 key drug (i.e. MRSA)
- Extensively drug-resistant (XDR)
  - Susceptible to 2 or less drug classes OR
  - Resistant to 1 or more key drugs
- Pandrug-resistant (PDR)
  - Resistant to all available drugs

IDSA 10 X ’20 Initiative

- Initiative for antibiotic development
  - Few antibiotic options available to treat highly resistant infections
- Launched in 2010
- 10 new antibiotics by 2020
- New drug approvals occurring

Types of Infections

- Hospital-acquired pneumonia
  - Healthcare-associated pneumonia (HCAP)
  - Ventilator-associated pneumonia (VAP)
- Bloodstream infections
  - Catheter-related and non-catheter related
- Catheter-associated urinary tract infections (CAUTIs)
- Surgical site infections

Hospital Acquired Infections

<table>
<thead>
<tr>
<th>HCAP/VAP</th>
<th>Bloodstream</th>
<th>CAUTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic criteria</td>
<td>May be associated with central venous catheter</td>
<td>Remove as soon as possible</td>
</tr>
<tr>
<td>Chest X-ray findings</td>
<td>Consider your source of infection</td>
<td>Culture only if patient is symptomatic</td>
</tr>
<tr>
<td>Temperature</td>
<td>ALWAYS send two peripheral blood cultures</td>
<td>Avoid irrigation, if possible</td>
</tr>
<tr>
<td>Leukocytosis or leukopenia</td>
<td>Catheter tip cultures should be correlated with blood culture findings</td>
<td>Maintains of treatment is REMOVAL of the Foley</td>
</tr>
<tr>
<td>Purulent secretions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory culture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tracheal aspirate or sputum culture (10^6 CFU/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchial-lavage (10^5 CFU/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronch-brush (10^4 CFU/mL)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Resistant Gram Negative Infections

- Extended Spectrum β-lactamases (ESBL)
- AmpC β-lactamases
- Carbapenem-resistant Enterobacteriaceae (CRE)
- MDR *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (assume carbapenem resistant)

Gram Negative Resistance

<table>
<thead>
<tr>
<th>ESBLs</th>
<th>AmpC β-lactamases</th>
<th>CRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Enzyme expression</td>
<td>• Inducible resistance</td>
<td>• K. pneumoniae Carbapenemases (KPCs)</td>
</tr>
<tr>
<td>• TEM-type</td>
<td>• E. aerogenes</td>
<td>• Most common mechanism in US</td>
</tr>
<tr>
<td>• SHV-type</td>
<td>• E. cloaca</td>
<td>• New Delhi &amp; VIM</td>
</tr>
<tr>
<td>• CTX-M-type</td>
<td>• Plasmid mediated</td>
<td>• Metallo-β-lactamases</td>
</tr>
<tr>
<td></td>
<td>• E. coli, K. pneumoniae, P. mirabilis</td>
<td>• OXA-48</td>
</tr>
</tbody>
</table>

Resistance Rates

<table>
<thead>
<tr>
<th>Pathogen and Antimicrobial Resistance</th>
<th>Resistance Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CLABSI</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em> and <em>Klebsiella oxytoca</em></td>
<td>12.8</td>
</tr>
<tr>
<td><em>Enterobacter cloacae</em></td>
<td>16.8</td>
</tr>
<tr>
<td><em>Citrobacter freundii</em></td>
<td>3.7</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>20.1</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>12.8</td>
</tr>
<tr>
<td><em>Providencia stuartii</em></td>
<td>4.0</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>62.6</td>
</tr>
<tr>
<td>MDR*</td>
<td>62.6</td>
</tr>
</tbody>
</table>
### Treatment Options

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESBL</strong></td>
<td>Meropenem&lt;br&gt; Doripenem&lt;br&gt; Imipenem</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolones&lt;br&gt; Ceftazidime/avibactam&lt;br&gt; Ceftolozane/tazobactam</td>
</tr>
<tr>
<td><strong>CRE</strong></td>
<td>Colistin&lt;br&gt; Fosfomycin&lt;br&gt; Ceftazidime/avibactam</td>
</tr>
<tr>
<td></td>
<td>Minocycline&lt;br&gt; Tigecycline</td>
</tr>
<tr>
<td><strong>XDR P. aeruginosa</strong></td>
<td>Colistin&lt;br&gt; carbapenem&lt;br&gt; Ceftolozane/tazobactam</td>
</tr>
<tr>
<td><strong>XDR A. baumannii (CRAB)</strong></td>
<td>Colistin&lt;br&gt; Tigecycline&lt;br&gt; Ampicillin/sulbactam (6 gm sulbactam/day)</td>
</tr>
</tbody>
</table>

*Can use a fluoroquinolone or an aminoglycoside if susceptible

---

### Polymixins

- Colistinmethate sodium (Polymixin E or “colistin”) & Polymixin B
- Discovered in late 1940s
- MOA: cationic detergent that disrupts the cell membrane → cell death
- **Dose** (adjust in renal impairment):
  - Colistin 2.5 – 5 mg/kg IV divided 2-4 x/day
  - Base IV dose on target steady state level in critically ill patients?
  - Colistin 100 mg nebulized q8h (for respiratory infections)
- **Bactericidal against most gram-negative bacilli**
- Historically, toxicity has limited use
  - Nephrotoxicity (10-60% of patients)
  - Neurotoxicity

---

**Tigecycline**

- **Mechanism of action**
  - Binds 30S ribosomal subunit, inhibiting protein synthesis
- **Bacteriostatic**
- **Dose**: 100 mg IV X 1 followed by 50 mg IV q12h
- **FDA approvals**
  - Community-acquired pneumonia
  - SSTIs
  - Complicated IAI
- **Broad spectrum of activity including gram negative bacteria and MRSA**
- **Increased mortality in meta-analysis of randomized control trials**

**Ceftolozane/Tazobactam**

- **New generation cephalosporin in combination with β-lactamase inhibitor**
- **FDA approved December 2014**
  - Complicated intra-abdominal infections
  - Complicated UTIs
- **Spectrum of Activity**
  - *P. aeruginosa*, including MDR and XDR pathogens
  - ESBLs
  - Some anaerobes, such as *Bacteroides* sp. (use in combination with metronidazole)
  - Not active for CRE

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPECT-cUTI</td>
<td>Ceftolozane/tazobactam (C/T) 1.5 g IV q8h vs levofloxacin 750 mg IV q24h X 7 days for cUTI or pyelonephritis</td>
<td>C/T was non-inferior to levofloxacin for composite microbiological cure and clinical cure (76.9% vs 68.4%, 95% CI 2.3-14.6) No major adverse drug reactions (ADRs) reported</td>
</tr>
<tr>
<td>ASPECT-IAI</td>
<td>C/T 1.5 g IV q8h plus metronidazole 500 mg IV q8h vs meropenem 1 g IV q8h X 6 – 14 days for cIAI</td>
<td>C/T was non-inferior to meropenem in clinical cure rates (83% vs 87.3%, 95% CI 0.81 – 0.54) Similar cure rates for C/T vs meropenem in ESBL infections (95.8% vs 88.5%, respectively) No difference in ADRs reported</td>
</tr>
<tr>
<td>ASPECT-NP</td>
<td>C/T 3 g IV q8h vs meropenem 1 g IV q8h X 6 – 14 days for VAP</td>
<td>Currently recruiting patients</td>
</tr>
</tbody>
</table>
**Ceftazidime/Avibactam**

- Third-generation cephalosporin in combination with novel β-lactamase inhibitor
- Dose: ceftazidime 2g/avibactam 500 mg given over 2h IV q8h
- FDA approved February 2015
- Complicated intra-abdominal infections
- Complicated UTIs
- Spectrum of Activity
  - Improved activity against KPC or OXA-48 carbapenemases
  - P. aeruginosa (not XDR)
  - ESBLs & AmpC producers
  - Some anaerobic activity (use in combination with metronidazole)
- Undergoing studies for nosocomial pneumonia

---

**Treatment Challenges**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapenems</td>
<td>Resistance, Role in combination therapy?</td>
</tr>
<tr>
<td>Colistin/Polymixin B</td>
<td>Optimal dosing &amp; therapeutic targets</td>
</tr>
<tr>
<td></td>
<td>Heteroresistance, Monotherapy?</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>Bacteriostatic, Efficacy in lungs, blood, urine</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Reduced efficacy outside of urinary tract</td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>Only available PO in US</td>
</tr>
<tr>
<td>Ceftazidime/avibactam</td>
<td>Limited data outside IAI &amp; UTI treatment</td>
</tr>
<tr>
<td>Ceftolozane/tazobactam</td>
<td></td>
</tr>
</tbody>
</table>

---

**Combination Therapy for Resistant Gram Negative Infections**

<table>
<thead>
<tr>
<th>CRAB</th>
<th>XDR Pseudomonas</th>
<th>CRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymixin base</td>
<td>Polymixin base</td>
<td>Polymixin base</td>
</tr>
<tr>
<td>Plus rifampin, fosfomycin, or carbapenem</td>
<td>plus carbapenem or Tigecycline, minocycline, sulbactam, or aminoglycoside</td>
<td>plus Tigecycline or aminoglycoside</td>
</tr>
<tr>
<td>Plus Tigecycline, minocycline, sulbactam, or aminoglycoside</td>
<td></td>
<td>Emergence of resistance documented on monotherapy</td>
</tr>
</tbody>
</table>
Bottom Line

- Optimal treatment of XDR and PDR gram-negative infections is unknown
- Combination therapy appears to be preferred for serious infections
  - Two active drugs for CRE (maybe imipenem/cilastatin)
  - Colistin plus carbapenem for CRAB
- Limited data for XDR pseudomonas (maybe ceftolozane/tazobactam)
- Future research is needed
  - Polymixin B
  - Dose optimization
  - Combination therapy
- Consider patient specific factors (infection site etc.)

Resistant Gram Positive Infections

- Staphylococcus Aureus
  - Methicillin resistant staphylococcus aureus (MRSA)
  - Vancomycin resistant staphylococcus aureus (VISA)
  - Vancomycin resistant staphylococcus aureus (VRSA)
- Other gram positives
  - Vancomycin resistant enterococcus (VRE)
  - Macrolide-resistant group A streptococci

Treatment Options for Invasive HAI

<table>
<thead>
<tr>
<th>Pathogen (VRE)</th>
<th>Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. Faecium (VRE)</td>
<td>Linezolid</td>
</tr>
<tr>
<td></td>
<td>Daptomycin*</td>
</tr>
<tr>
<td></td>
<td>Quinupristin/dalfopristin</td>
</tr>
</tbody>
</table>

| S. Aureus (MRSA) | Vancomycin |
| S. Aureus (VISA & VRESA) | Linezolid |
| S. Aureus (VISA & VRESA) | Daptomycin* |

*Daptomycin ≠ indicated in the treatment of pneumonia
Staphylococcus Aureus

- MRSA rates up to 60% in USA
- Resistance beyond MRSA is emerging
  - “Daptomycin non-susceptible”
- Minimum inhibitory concentration (MICs) cutoffs for vancomycin
  - Susceptible MIC ≤ 2 mcg/mL
  - Intermediate (VISA) MIC > 4-8 mcg/mL
  - Resistant (VRSA) MIC > 16 mcg/mL
- Higher rate of treatment failure with vancomycin MIC > 1.5 mcg/mL
- 13 VRSA isolates identified in United States

Other MRSA Treatment Options

- Clindamycin
- Tetracyclines
- TMP/SMX
- Tigecycline
  - Increased mortality for bacteremia
- Quinupristin/dalfopristin
  - Lots of ADRs

Old Drug Classes…New Agents for MRSA

<table>
<thead>
<tr>
<th>Lipopeptides/Glycopeptides</th>
<th>Oxidolidindiones</th>
<th>Cephalosporin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>Linezolid</td>
<td>Ceftaroline</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Tedizolid</td>
<td></td>
</tr>
<tr>
<td>Telavancin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dalbavancin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oritavancin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Lipoglycopeptides**

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Dose</th>
<th>Activity</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telavancin</td>
<td>10 mg/kg IV q24h</td>
<td>MSSA, MRSA, E. faecalis, S. pyogenes, S. agalactiae, S. anginosus</td>
<td>Skin and skin soft tissue infections (SSTIs) &amp; VAP</td>
</tr>
<tr>
<td>Oritavancin</td>
<td>1200 mg IV X 1</td>
<td>MSSA, MRSA, E. faecalis, S. pyogenes, S. agalactiae</td>
<td>SSTIs</td>
</tr>
<tr>
<td>Dalbavancin</td>
<td>1 gm IV X 1 followed by 500 mg IV X 1 7 days later</td>
<td>MSSA, MRSA, S. pyogenes, S. pneumoniae, E. faecalis</td>
<td>SSTIs</td>
</tr>
</tbody>
</table>

**Lipoglycopeptides versus Vancomycin**

**Advantages of Newer Agents**
- Less frequent dosing
- Routine monitoring is not required
- Higher HAP cure rates with telavancin versus vancomycin in patients with MIC > 1 mg/L

**Disadvantages**
- Cost
- Limited clinical experience
- Increased nephrotoxicity with telavancin

**Ceftaroline**
- Ceftaroline fosamil prodrug for ceftaroline
- Approved for SSTI and community-acquired pneumonia
- Dosing: 600 mg IV q12h over 1 hour (dose adjust for renal impairment)
- "Fifth-generation cephalosporin"
  - Broad spectrum of activity
  - Expanded gram positive activity against MRSA, VISA/VRSA
  - No pseudomonal/ESBL coverage
Tedizolid
- Oxazolidinone similar to linezolid
- Approved for SSTIs
- Dosing 200 mg IV/PO q24h
- Advantages
  - Improved safety profile compared to linezolid
  - Once daily dosing
- Role in therapy?

Combination Therapy for S. Aureus
- Synergistic combinations
- Primarily used as salvage therapy for persistent bacteremias or endocarditis
- Vancomycin
  - Plus gentamicin or rifampin
  - Plus antistaphylococcal beta lactam
- Daptomycin IV 8-10 mg/kg/day
  - Plus antistaphylococcal beta lactam
  - Plus vancomycin
  - Plus TMP/SMX

Bottom Line
- Source control is a MUST
- Vancomycin may be used if MIC < 2
  - Consider alternative agent if persistently positive blood cultures
  - Etest versus automated test
- Role for new lipoglycopeptides (oritavancin, dalbavancin)?
  - Outpatient treatment option for S. aureus SSTIs
- Telavancin, ceftaroline, or combination therapy may be considered for salvage therapy
- Future research is needed
Summary

- Resistant infections are common inpatient
- Consider source/severity of infection when determining optimal therapy
- Recent antimicrobial approvals
  - ...although more are still needed
  - Clinical experience is lacking with these agents
  - Cost may be prohibitive
- Need for research/optimization of “older” agents (i.e. polymixins etc.)

Patient Case - GM

- GM is a 42 yo male presenting to the ICU with severe sepsis.
- Vital signs are stable after 2L crystalloid are administered. BP 120/75 mmHg, RR 18, HR 86. WBC 14. All other labs are WNL.
- PMH significant for IVDU, hepatitis B, & alcohol abuse.
- Vancomycin 25 mg/kg IV LD, followed by 15 mg/kg maintenance dose plus piperacillin/tazobactam 4.5 g IV q6h are started empirically in the emergency department. Two blood cultures are taken prior to antibiotic administration.

Patient Case - GM

- Hospital Day 3: 2/2 blood cultures positive (final) with S. aureus
- S. aureus susceptibilities reported are as follows:
  - Vancomycin MIC = 2 (S)
  - Daptomycin MIC ≤ 2 (S)
  - Oxacillin MIC ≥ 8 (R)
  - Linezolid MIC ≥ 2 (S)
- TTE obtained with limited visualization of the heart valves; blood cultures repeated
Patient Case - GM

Which of the following treatment recommendations would you make to the team following release of susceptibility results?

A. Continue vancomycin; discontinue piperacillin/tazobactam
B. Discontinue vancomycin and piperacillin/tazobactam; start daptomycin 4 mg/kg IV q24h
C. Continue vancomycin plus piperacillin/tazobactam
D. Discontinue vancomycin and piperacillin/tazobactam; start tigecycline 100 mg X 1, followed by 50 mg IV q12h

Patient Case - GM

GM has now been admitted X 8 days. Daily blood cultures have remained positive X 6 days, despite vancomycin treatment (all troughs > 15 mcg/dL)

At this point what recommendations do you make to the team?

A. No change; continue vancomycin
B. Continue vancomycin; add rifampin
C. Discontinue vancomycin; start daptomycin 8 mg/kg IV q24h
D. Discontinue vancomycin; start linezolid 600 mg IV q12h

Patient Case - GM

1. What other treatment regimen may be appropriate as salvage therapy for this patient?
   A. Ceftaroline plus daptomycin
   B. Ceftolozane/tazobactam
   C. TMP/SMX
   D. Vancomycin plus gentamicin

2. What other diagnostic testing would you recommend for this patient?
Patient Case - JJ

- JJ is a 72 yo male admitted to the hospital 65 days ago. JJ has had a complicated ICU course including respiratory failure 2/2 to septic shock and ARDS which resulted in tracheostomy placement and acute on chronic kidney failure now on intermittent hemodialysis. He has also had recurrent pseudomonal pneumonias treated with piperacillin/tazobactam, cefepime, & meropenem.
- Current vital signs: Tm 99.0°F, BP 100/63 mmHg, RR 33, HR 92. CXR shows new RLL infiltrate. A bronchoalveolar lavage (BAL) culture taken 2 days ago shows drug resistant pseudomonas.

Patient Case - JJ

Pseudomonas susceptibility results are as follows:

- Amikacin  
  MIC = 8 mcg/mL (S)
- Piperacillin/tazobactam  
  MIC = 64 mcg/mL (R)
- Tobramycin  
  MIC > 16 mcg/mL (R)
- Cefepime  
  MIC = 16 mcg/mL (I)
- Aztreonam  
  MIC > 32 mcg/mL (R)
- Gentamicin  
  MIC > 16 mcg/mL (R)
- Meropenem  
  MIC > 8 mcg/mL (R)

*The ID team request colistin susceptibility results; MIC 1 mcg/mL (S)

Patient Case - JJ

How would you classify the extent of resistance of JJ’s pseudomonal infection?

A. Multi-drug resistant
B. Extensively-drug resistant
C. Pan-drug resistant
D. Other
Patient Case - JJ

What treatment recommendation would you make for JJ?

A. Amikacin 15 mg/kg IV q24h monotherapy
B. Colistin 1.5 mg/kg IV q24h monotherapy
C. Colistin 1.5 mg/kg IV q24h plus piperacillin/tazobactam 2.25g IV q8h
D. Ceftaroline 600 mg IV q12h

Questions?

Kaitlin McGinn, PharmD
Assistant Clinical Professor, Critical Care
Auburn University, Harrison School of Pharmacy
kam0082@auburn.edu