Tackling Drug Resistant Infections: Mechanisms of Antimicrobial Resistance

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UMKC
Kansas City, MO
COI Statement

• Grant Funding
  – Johnson and Johnson
  – Cubist

• No other potential conflicts
“We have a Problem Houston”

• National Nosocomial Infection Surveillance System (NNIS)
  – UTI > Pneumonia > BSI
  – But 67% of HAI deaths due to pneumonia and BSI

• Most common lethal organisms
  – E. coli, Pseudomonas, MRSA
  – Honorable mention to acinetobacter

• Absolute number of such HAIs up in past 10 yrs
  – MRSA the major factor < 18 yos

Klevenes et al. CID 2008 47:927-30
Empiric Antibiotics (Abx) for Hospital Acquired Infections (HAI)

Goal: Reduced mortality and minimized resistance
- Early aggressive, appropriate empiric Rx and de-escalation

1. Severe sepsis or septic shock - Critical determinants
   - Initial appropriate Abx and source control

2. HAI bloodstream infection
   - Appropriate empiric Abx covers MDR gram-neg bacteria and MRSA

3. Any serious HAI from suspected gram-neg bacteria
   - Appropriate empiric Rx = dual coverage including aminoglycoside

4. Vancomycin obsolete for treating MRSA

5. All immunocompromised patients’ infections
   - Cover for hospital acquired pathogens until proven otherwise

Hospital Care Associated Infection Summit. CID 2008. Oct; 47 (suppl 2): S57
Case 1

• 15 yo CF patient with OLT 3 yrs ago
  – Still on modest immune suppression
  – Pulmonary exacerbations X 5 in past 2 yrs
    • Frequent broad spectrum antibiotics used
    • No central lines in place

• Presenting Problem:
  – Fever, emesis and diarrhea initially
  – Mental status changes later
  – Shock with respiratory failure now

– Previously colonized with MRSA and VRE
Empiric Antibiotics Case 1

• Gm positive coverage
  – Vancomycin, Linezolid, or Clindamycin?

• Gram negative coverage
  – Ceftazidime, cefepime, meropenem, or pipericillin/tazobactam?
  – Add gentamicin or not?
Antibiotic Mechanisms

**Cell Wall Synthesis**
- Vancomycin
- Penicillins
- Cephalosporins
- Monobactams
- Carbapenems

**DNA Gyrase (Replication)**
- Quinolones
- Nalidixic Acid

**RNA Dependent DNA Synthesis**
- Rifampin

**Protein Synthesis 50s ribosomes**
- Macrolides
- Azolides
- Clindamycin
- Ketolides

**Protein Synthesis 30s ribosomes**
- Tetracyclines
- Aminoglycosides
- Spectinomycin

**Folic Acid Path**
- Trimethoprim
- Sulfonamides
- PABA

**Cell Membrane**
- Polymyxins

**Initiation Complex**
- Linezolid (Unique)

**30s ribosomes**

**50s ribosomes**

**DNA**

**mRNA**
Bacterial Tools For Resistance

1. Reduce Abx access to target
   - Less entry – Porins
   - More exit – Efflux pumps, e.g. Mef A

2. Alter Abx target
   - PBPs, Topoisomerase, gyrase, DHFA,
   - Ribsomal binding sites, e.g. ErmB, ErmT

3. Inactivate Abx
   - Beta lactamases, e.g. TEM-1
     • ESBL or Amp C
   - Aminoglycosidase, e.g. Adenyltransferase
Empiric Antibiotics Case 1

- **Gm positive coverage**
  - Linezolid

- **Gram negative coverage**
  - Cefepime,
  - Add gentamicin
Culture Results

- Blood Cultures X 2
  - GPC at 8 hours

MRSA
CA- or HA-MRSA?

<table>
<thead>
<tr>
<th>BC MIC</th>
<th>ug/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCN</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Oxa</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Amox/clav</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Clinda</td>
<td>8</td>
</tr>
<tr>
<td>Erythro</td>
<td>16</td>
</tr>
<tr>
<td>Cipro</td>
<td>8</td>
</tr>
<tr>
<td>T/S</td>
<td>40</td>
</tr>
<tr>
<td>Vanco</td>
<td>1.0</td>
</tr>
<tr>
<td>Rifampin</td>
<td>0.5</td>
</tr>
<tr>
<td>Linezolid</td>
<td>1.0</td>
</tr>
<tr>
<td>Gent</td>
<td>&lt;256</td>
</tr>
</tbody>
</table>
MRSA Antibiogram, CMH 2007 -08

* Not useful as sole therapy, resistance almost immediate

% Susceptible

Cj Harrison, Unpublished
<table>
<thead>
<tr>
<th>health care contact</th>
<th>HA-MRSA</th>
<th>CA-MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>health care contact</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>mean age at infection</td>
<td>older</td>
<td>younger</td>
</tr>
<tr>
<td>skin and soft tissue infections</td>
<td>35%</td>
<td>75%</td>
</tr>
<tr>
<td>antibiotic resistance</td>
<td>many agents</td>
<td>some agents</td>
</tr>
<tr>
<td>resistance gene</td>
<td>SCCmec Types I, II, III</td>
<td>SCCmec Type IV, V</td>
</tr>
<tr>
<td>strain type</td>
<td>USA 100 and 200</td>
<td>USA 300 and 400</td>
</tr>
<tr>
<td>PVL toxin gene</td>
<td>rare (5%)</td>
<td>frequent (almost 100%)</td>
</tr>
</tbody>
</table>
Inducible Macrolide-Lincosamide Resistance in *S. aureus* “D-Zone”
Decelerate Antibiotics Case 1

• Gm positive coverage – HA-MRSA
  – Linezolid
  – Consider rifampin

• Gram positive synergy?
  – Add gentamicin
**Glycopeptide class**

- Spectrum of activity:
  - Gram-positives
    - Staphylococcus (MRSA)
    - Enterococcus
    - Streptococci

- Elimination by renal route
- PK
  - 2-3 compartment drug
  - T1/2 h 6-12 h

**Vancomycin**

*Recent reports of treatment failures or very slow responses*
Vanco Resistance
How Vanco Works

Vancomycin-Sensitive Bacterium
Cell Wall

Vancomycin Binds, Cell Wall Does Not Form

Vancomycin-Resistant Bacterium
Cell Wall

Vancomycin Cannot Bind, Cell Wall Unaffected

Legend:
- Vancomycin
- Alanine-Alanine
- Alanine-Lactate
MRSA vs Vancomycin
“MIC CREEP”

- CLSI recently lowered vanco breakpoints
  - Susceptible \( \leq 2 \text{ ug/mL} \)
  - Intermediate 4-8 \( \text{ug/mL} \)
  - Resistant \( \geq 16 \text{ ug/mL} \)
- Vanco resistance (VRSA) remarkably rare
  - Vanco-intermediate (VISA) also infrequent
- Nexus of 2 factors raises concern
  1. MIC creep
     - gradually reduced susceptibility to vancomycin
  2. Poor response when MICs of 1-2.0 \( \text{ug/mL} \)
     - Particularly at 2 \( \text{ug/mL} \)

Derezenski. CID 2007; 44:1543–8
# Choose Wisely

<table>
<thead>
<tr>
<th>Vancomycin MIC (ug/ml)</th>
<th>Breakpoint category</th>
<th>Would you use vanco?</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5</td>
<td>Susceptible</td>
<td>a. Yes / No</td>
</tr>
<tr>
<td>0.5</td>
<td>Susceptible</td>
<td>b. Yes / No</td>
</tr>
<tr>
<td>1.0</td>
<td>Susceptible</td>
<td>c. Yes / No</td>
</tr>
<tr>
<td>2.0</td>
<td>Susceptible</td>
<td>d. Yes / No</td>
</tr>
<tr>
<td>4.0</td>
<td>Intermediate</td>
<td>e. Yes / No</td>
</tr>
<tr>
<td>8.0</td>
<td>Intermediate</td>
<td>f. Yes / No</td>
</tr>
</tbody>
</table>
Hacking away at Vanco

- Peak concentration = 30 mg/L
- 50% bound = 15 mg/L
- Dimerization = 7.5 mg/L
- Tissue barriers = 0.375 – 5.0
- MIC$_{90}$ of MRSA = 2.0 mg/L

- If MIC = >0.5 mg/L and inoculum high
  - Confidence in clinical success is less
<table>
<thead>
<tr>
<th></th>
<th>Vanc MIC &lt; 1</th>
<th>Vanc MIC = 1-2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Success rate</strong></td>
<td>55.6%</td>
<td>9.5%</td>
</tr>
<tr>
<td>(Sakoulas et al 2004)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hospital LOS</strong></td>
<td>10 days</td>
<td>14 days</td>
</tr>
<tr>
<td>(MacLayton et al 2006)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>End of therapy response</strong></td>
<td>85%</td>
<td>62%</td>
</tr>
<tr>
<td>(Hidayat et al 2006)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Eradication rate</strong></td>
<td>77%</td>
<td>21%</td>
</tr>
<tr>
<td>Moise et al 2007</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
New Trough Vanco Recs

• Traditional
  - 5-10 ug/mL

• Since MIC Creep
  - 10-15 ug/mL

Lodise et al AAC 2008 52:1330
High Dose Vanco Adult Toxicity

Lodise et al. AAC 2008;52:1330-6
### Other Culture Results

- **Urine culture**
  - *E. faecium*

- **Stool Culture**
  - *E. faecium*

<table>
<thead>
<tr>
<th><strong>Urine and Stool</strong></th>
<th><strong>MIC ug/mL</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>PCN</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Clinda</td>
<td>8</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>-</td>
</tr>
<tr>
<td>Cipro</td>
<td>8</td>
</tr>
<tr>
<td>T/S</td>
<td>-</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>8</td>
</tr>
<tr>
<td>Rifampin</td>
<td>-</td>
</tr>
<tr>
<td>Linezolid</td>
<td>1.0</td>
</tr>
</tbody>
</table>

VRE
### Genes Conveying Vanco Resistance in Enterococcus

<table>
<thead>
<tr>
<th>Phenotype Vanco MIC (µg/mL)</th>
<th>VanA</th>
<th>VanB</th>
<th>VanC</th>
<th>VanD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teico MIC (µg/mL)</td>
<td>64 to &gt;1000</td>
<td>4 to 1000</td>
<td>2 to 32</td>
<td>64</td>
</tr>
<tr>
<td>Expression</td>
<td>Inducible</td>
<td>Inducible</td>
<td>Inducible</td>
<td>Inducible</td>
</tr>
<tr>
<td>Location of R genes</td>
<td>Plasmids</td>
<td>Chromosome (plasmids)</td>
<td>Chromosome</td>
<td>?</td>
</tr>
<tr>
<td>Transfer by conjugation</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mobile element</td>
<td>Tn 1546</td>
<td>Tn 1547</td>
<td>–</td>
<td>?</td>
</tr>
<tr>
<td>Modified target</td>
<td>d-Ala-d-Lac</td>
<td>d-Ala-d-Lac</td>
<td>d-Ala-d-Ser</td>
<td>d-Ala-d-Lac</td>
</tr>
<tr>
<td>Species</td>
<td><em>E. faecalis</em></td>
<td><em>E. faecalis</em></td>
<td><em>E. faecalis</em></td>
<td><em>E. faecium</em></td>
</tr>
<tr>
<td></td>
<td><em>E. mundtii</em></td>
<td></td>
<td><em>E. faecium</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>E. faecium</em></td>
<td></td>
<td></td>
<td><em>E. faecium</em></td>
</tr>
<tr>
<td></td>
<td><em>E. raffinosus</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>E. avium</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>E. gallinarum</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>E. durans</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>E. casseliflavus</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>E. fallinarum</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>E. casselilavus</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>E. flavescens</em></td>
<td></td>
</tr>
</tbody>
</table>
Enterococcal Vancomycin Resistance

Conveys resistance by producing a modified D-ala D-ala molecule to which vancomycin cannot bind.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Genotype (resistance operon present)</th>
<th>Vancomycin MIC (µg/mL)</th>
<th>Teicoplanin MIC (µg/mL)</th>
<th>Expression</th>
<th>Ability to transfer resistance</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>VanA</td>
<td>vanA</td>
<td>64-&gt;1000</td>
<td>16-512</td>
<td>Inducible</td>
<td>Yes</td>
<td>Enterococcus faecium, E faecalis, E avium, E gallinarum, E durans, E mundtii, E casseliflavus, E raffinosus, E hirae</td>
</tr>
<tr>
<td>VanB</td>
<td>vanB</td>
<td>4-1000</td>
<td>0.25-2</td>
<td>Inducible</td>
<td>Yes</td>
<td>Enterococcus faecium, E faecalis, E gallinarum, E durans</td>
</tr>
</tbody>
</table>
New Sheriffs in Town?

Daptomycin - cyclic lipopeptides
Not for pulmonary issues
Surfactant inactivates

Linezolid - Oxazolidinone
Expensive
Anemia, neutropenia, Thrombocytopenia

Tigecycline
Not FDA Pediatric approved

Ceftobiprole - 5th generation Cephalosporin
Experimental

New Sheriffs in Town?
Dalbavancin
Semi-synthetic glycopeptide

• Long ½ life = 200-300hrs – once weekly dosing
• In vitro superior to vancomycin and teicoplanin
• Excellent activity vs staphylococci
  – Bactericidal for staphylococci
  – Including MRSA, some GISA, and CoNS
  – Resistance to this is not readily developed in vitro
• Active vs teicoplanin-nonsusceptible CoNS
  – MIC range, 0.03-0.25 mug/mL
• Inhibits van B enterococci
  – MIC range, 0.03-0.12 mug/mL
• Van A enterococcal strains susceptible
  – MIC(50), 16 mug/mL
Case 2

- 7 yo s/p spinal cord injury
  - Neurogenic bladder
  - Multiple UTIs in past 3 yrs
  - Last 2 UTIs treated with ceftazidime
  - Macrodantin prophylaxis

- Problem:
  - High fever, appears ill, hypotension
  - Catheterized urine specimen has pyuria and gram negative rods
Empiric Antibiotics Case 2

• Gm positive coverage
  – Vancomycin, Linezolid, or Clindamycin?

• Gram negative coverage
  – Ceftazidime, cefepime, meropenem, or pipericillin/tazobactam?
  – Add aminoglycoside or not?
Empiric Antibiotics (Abx) for Hospital Acquired Infections (HAI)

Goal: Reduced mortality and minimized resistance
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1. Severe sepsis or septic shock - Critical determinants
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Hospital Care Associated Infection Summit. CID 2008. Oct; 47 (suppl 2): S57
Empiric Antibiotics Case 2

- Gm positive coverage
  - Vancomycin? YES

- Gram negative coverage
  - Ceftriaxone, Meropenem, or pipericillin/tazobactam? Meropenem
  - Add aminoglycoside? YES
Culture Results

- Blood Cultures X 2
  - GNR at 12 hours

- Urine culture
  - GNR at 24 hours

E.Coli
  ESBL producer

<table>
<thead>
<tr>
<th>BC and Urine Cult</th>
<th>MIC ug/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amp</td>
<td>&gt;64</td>
</tr>
<tr>
<td>Pip/Tazo</td>
<td>2.0</td>
</tr>
<tr>
<td>Meropenem</td>
<td>0.5</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>&gt;64</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>&gt;256</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>&gt;256</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>16</td>
</tr>
<tr>
<td>Cipro</td>
<td>8</td>
</tr>
<tr>
<td>T/S</td>
<td>320</td>
</tr>
<tr>
<td>Amikacin</td>
<td>1.0</td>
</tr>
</tbody>
</table>

E.Coli is an ESBL producer.
Decelerate Antibiotics Case 2

• Gm positive coverage
  – None

• Gram negative coverage
  – Meropenem, or pipericillin/tazobactam
  – Add aminoglycoside
Beta-Lactam Vulnerable Site

Beta-lactamase site of Hydrolysis

Acyl Side Chain

Beta-Lactam Ring

Thiazolidine Ring

Dihydrothiazidine Ring

Beta-lactamase site of Hydrolysis
Beta-Lactam Resistance in Gram(-) Bacteria

Intramembranous β-lactamase inactivates β-lactam antibiotics

Clavulanic acid irreversibly binds β-lactamase protecting β-lactam antibiotics

Peptidoglycan cell wall

2 Plasma membranes

Porin mutation: Reduced size of channels inhibits antibiotic entry
Extended Spectrum $\beta$-Lactamases (ESBLs)

- Hydrolyze mono- & $\beta$-lactam antibiotics
  - From TEM-1 or SHV-1 broad-spectrum $\beta$-lactamases
    - New families: CTX-M and OXA enzymes
    - Often on plasmids & transferable strain-strain or spp.-spp.
- Co-habit plasmids with AmpC $\beta$-lactamases
- Suspect when MIC >2mg/L for 3rd gen Cephs
- Recent increased prevalence
  - Classic - *E. coli* and *K. pneumoniae*
  - New - *Enterobacter, pseudomonas, proteus, salmonella, Citrobacter* spp, *Morganella morganii, Serratia marcescens, Shigella dysenteriae, Burkholderia cepacia, and Capnocytophaga*

Patterson J. Ped Infect Dis J: 21(10) 2002 pp 957-959
ESBL Confirmation

• Disk Diffusion Methods
  – Home made
    • Augmentin® 60 mg disc or Timentin® 85 mg disc near cefotaxime 5 mg disc
    • Clear synergy zone or elliptical clear area between discs
  – BBL Kit 90-94% sensitive

• ESBL Etest
  – 98% sensitive with cefepime-clavulanate
  – 83% with cefotaxime-clavulanate
  – 74% with ceftazidime-clavulanate

• Automated systems
  – Vitek

**ESBL Tests**

Figure 1a: Organism showing enhanced zone of inhibition between ceftazidime/cefotaxime and clavulanic acid disc indicating positive ESBL.
Clinical - ESBL

- Clinical Infections - Singly or outbreaks
  - Critical care units, CF & Transplant Patients
  - Increase Rx cost prolong hospital stays

- Important reservoirs
  - Chronic care facility patients
  - Ambulatory patients w chronic conditions

Drugs for ESBL Producers

- **Meropenem** – best bet (95%)
  - Generally resistant to ESBL
  - Penetrates CSF, bone, peritoneal fluid
  - PD requirement – 30% time > MIC
- **Piperacillin/tazobactam** (~85%)
- **Aminoglycosides** – often resistant
  - Tobramycin more reliable in some locales
- **Cephamycins** – N.B. AmpC inactivates these
  - Cefoxitin or cefotetan
- **Quinolones**- increasing resistance
  - Ciprofloxacin only Ped approved quinolone - for complicated UTI’s
- **NEVER** Cephalosporins
  - 54% fail therapy even when MIC ≤8 μg/ml

Case 3

- 6 mos old former 24-weeker
  - Mother is Iraq Army Veteran
  - Hospitalized since birth
  - S/P IVH, NEC, chronic lung disease
  - VP shunt for hydrocephalus
  - Current shunt is his 3rd
  - Recent *S. aureus* infection
    - External ventriculostomy in place X 7 days

- Problem:
  - New fever
  - Ventricular fluid has 1,000 WBC, 90% PMN and gram negative rods on smear
Empiric Antibiotics Case 3

• Gm positive coverage
  – Vancomycin, Linezolid, or Clindamycin?

• Gram negative coverage
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• Gram negative coverage
  – Ceftazidime, cefepime, meropenem, or pipericillin/tazobactam?
  – Add aminoglycoside or not?
Culture Results

- Blood Cultures X 2
  - GNR at 12 hours

- Urine culture
  - GNR

Acinetobacter baumannii
Amp C and ESBL producer

BC and MIC Urine Cult ug/mL
- Amp >64
- Pip/Tazo 2.0
- Meropenem 0.5
- Cefazolin >64
- Cefotaxime >256
- Ceftazidime >256
- Gentamicin 16
- Cipro 8
- T/S 320
- Amikacin 1.0
- Colistin 0.25
Decelerate Antibiotics Case 3

• Gm positive coverage
  – None

• Gram negative coverage
  – Colistin
  – Amikacin
A. Baumannii – A.K.A

- Achromobacter anitratus
- Achromobacter mucosus
- Alcaligenes haemolysans
- Bacterium anitratum
- Diplococcus mucosus
- Herellea vaginicola
- Micrococcus calcoaceticus
- Mima polymorpha
- Moraxella Iwoffi
  - Var. glucidolytica
- Neisseria winogradskyi
**A. baumannii** Molecular Resistance Mechanisms

- Various resistance phenotypes
  - Mutations of PBPs
  - Alterations of membrane permeability
- β-lactamases most common
  - Chromosomal or on plasmids
  - Class A, B, and D β-lactamases
  - Extended-spectrum β-lactamase (ESBL)
Resistance to Fluoroquinolones

Mutant DNA gyrase & topoisomerase enzymes
Fluoroquinolone unable to block DNA supercoiling or packaging

Porin Mutation: Reduces cell wall permeability, inhibits entry

Bacterial efflux pumps
Fluoroquinolone excreted
**AmpC Inducible β-lactamases**

- **Parent** = Chromosomal but now on Plasmid
  - Repressed until see substrate → hyper-producers
- **Functional group 1** (Bush *et al*, 1995)
- Not inhibited by clavulanic acid – may also have ESBL
  - Enterobacter, *Serratia*, *Citrobacter*, *Aeromonas*, *Providencia*, *Morganella*, *Hafnia* – “ESCAPPM”
  - Resistant to 3rd generation cephs & amox/clav or ticar/clav
- **Functional group 2e**
  - Inhibited by clavulanic acid
  - *Proteus vulgaris*
  - Susceptible to: Clav combos, ceftzidime
- **Test**: Flat inhibitory zone of cefotaxime 5 mg disc near imipenem 10 mg disc
MDR A. baumannii

• Traditionally
  – Nosocomial pneumonia

• New
  – CNS, skin and soft tissue, and bone

• typically resistant to
  – Aminoglycosides
  – Antipseudomonal penicillins
  – Carbapenems
  – Cephalosporins
  – Quinolones.
It’s the “Next Big Bad Thing”

- **A. baumannii** strains
  - Often resistant to all known antibiotics
  - Uncanny prolonged survival in hospital
    - Up to 5 months
    - Potentiates ability for nosocomial spread
  - A sentinel event
    - Needs attention Infection Control Team

- Colistin plus amikacin here
  - Consider intrathecal if not clearing soon

- Tigecycline, carbapenem or cefepime may have utility in some cases
Empiric Antibiotics (Abx) for Hospital Acquired Infections (HAI)

Goal: Reduced mortality and minimized resistance
- Early aggressive, appropriate empiric Rx and de-escalation

1. Severe sepsis or septic shock - Critical determinants
   - Initial appropriate Abx and source control

2. HAI bloodstream infection
   - Appropriate empiric Abx covers MDR gram-neg bacteria and MRSA

3. Any serious HAI from suspected gram-neg bacteria
   - Appropriate empiric Rx = dual coverage including aminoglycoside

4. Vancomycin obsolete for treating MRSA

5. All immunocompromised patients’ infections
   - Cover for hospital acquired pathogens until proven otherwise

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