Antibiotics for the Hospitalized Patient

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A 67 year old man with a history of congestive heart failure is admitted to the hospital with a diagnosis of community acquired pneumonia.

Etiology of CAP Requiring Hospital Admission

- Culture blood, sputum, nasopharyngeal secretions
- Sputum by real-time quantitative PCR for S. pneumoniae, H. influenzae, M catarrhalis and nasopharyngeal specimens by PCR
- Serologic testing for M. pneumoniae, C. pneumoniae, respiratory viruses
- Urine antigen assay for pneumococcus, Legionella

(Clin Infect Dis 2010; 50: 202)
The Response to Multidrug-Resistant S. pneumoniae

Fluoroquinolones and ceftriaxone, agents with superb activity versus MDR S. pneumoniae, however, with an “unnecessary” spectrum vs gram negative pathogens, are recommended by the Infectious Diseases Society of America/American Thoracic Society for the empirical treatment of hospitalized patients with community acquired pneumonia.

(Clin Infect Dis 2007; 44: S27-72)

IDSA/ATS Recommended Antibiotics for CAP

Non-ICU
1. An IV or PO respiratory fluoroquinolone (levofloxacin (750mg), moxifloxacin, gemifloxacin)
   OR
2. An IV beta-lactam (ceftriaxone, cefotaxime, ampicillin) plus an IV macrolide

ICU
1. An IV beta-lactam (ceftriaxone, cefotaxime, ampicillin-sulbactam) plus an IV fluoroquinolone (levofloxacin, moxifloxacin) or IV azithromycin
Seven days into an empirical course of ceftriaxone and azithromycin, he experiences respiratory decompensation associated with increased oxygen requirements and a new infiltrate (i.e. HAP). Multiple blood cultures are positive for an aerobic gram-negative rod.

Which of the following agents would be least likely to be active in a patient (receiving ceftriaxone) with gram negative sepsis?

1. Tigecycline
2. Cefepime
3. Piperacillin-tazobactam
4. Ertapenem
5. Imipenem

Cephalosporins

- First generation: cefazolin (PEK: Proteus mirabilis, E. coli, Klebsiella)
- Second generation: cefuroxime, cefotetan (cefotetan once again available) (HNPEK: H. influenzae and 1st GC-resistant PEK)
- Third generation: cefotaxime, ceftriaxone, ceftazidime (HNPEKS: S. marcescens); ceftazidime is the only reliable antipseudomonal 3rd GC
- Fourth generation: cefepime
- Fifth generation: cefaroline, ceftobiprole (GNRs similar to a 3rd generation agent AND MRSA)
Third-generation Agents (Ceftriaxone): Holes in Gram-negative Spectrum

- Citrobacter
- Acinetobacter
- Pseudomonas (however, ceftazidime strong)
- Enterobacter AND ESBLs
- Stenotrophomonas (and/or Serratia)

And then there are the ESKAPE bacteria

- *Enterococcus faecium*
- *Staphylococcus aureus*
- *Klebsiella species*
- *Acinetobacter baumannii*
- *Pseudomonas aeruginosa*
- *Enterobacter species*
  (Clin Infect Dis 2009; 48: 1)

Which of the following statements is correct regarding ESBL-producers?

1. Usual in vitro susceptibility testing does not reliably identify ESBL-producers
2. All bacteremic patients with *E. coli* and *K. pneumoniae* should undergo confirmatory testing for ESBL
3. Often are associated with aminoglycoside, fluoroquinolone, trimethoprim-sulfamethoxazole resistance
4. All of the above
Extended Spectrum Beta-Lactamase (ESBL): Key Points

• β-lactamases hydrolyze third-generation cephalosporins and aztreonam yet are inhibited by clavulanic acid
• Often plasmid encoded and frequently carry genes encoding resistance to other drug classes (e.g. aminoglycosides, fluoroquinolones)
  (Ann Pharmacother 2007; 41: 1427)

Extended Spectrum Beta-Lactamase (ESBL): Key Points

• ESBL-producing organisms may appear to be susceptible to extended-spectrum cephalosporins, however, treatment with these agents is associated with high clinical failure rates
• Detection of ESBL by the clinical microbiology laboratory historically difficult. Presence of ESBL centers upon enhancement of extended-spectrum cephalosporin activity in the presence of clavulanic acid
  (Ann Pharmacother 2007; 41: 1427)

Identification of ESBL Producer (CDC)
Revised and New CLSI Breakpoints

<table>
<thead>
<tr>
<th>Drug</th>
<th>New “Susceptible” MIC</th>
<th>Old “Susceptible” MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime</td>
<td>≤8</td>
<td>≤8</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>≤1</td>
<td>≤8</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>≤1</td>
<td>≤8</td>
</tr>
</tbody>
</table>


Extended Spectrum Beta-Lactamase (ESBL): Key Points

- Imipenem and meropenem (and doripenem) are the most reliable agents in the treatment of ESBL
- While active in vitro, ertapenem, tigecycline, colistin, have limited clinical experience but are potential options (Ann Pharmacother 2007; 41: 1427)

Gram-negative Activity: Cefepime

(* = expanded coverage over ceftriaxone)

- H. influenzae
- Enterobacter*
- Neisseria
- Proteus (and Pseudomonas*)
- E. coli (but does not reliably cover ESBL-producing isolates)
- Citrobacter*
- Klebsiella (but does not reliably cover ESBL-producing isolates)
- Serratia
Efficacy and Safety of Cefepime: a Systematic Review and Meta-Analysis

- Revealed increased mortality associated with the use of cefepime.
- FDA subsequently issued a warning


Meta-Analysis of a Possible Signal of Increased Mortality Associated with Cefepime Use

- Trial-level analysis based on 88 trials (9467 cefepime patients and 8288 comparators)
  - All cause morality: cefepime (6.21%) and comparator (6.00%)
- Patient level-level analysis based on 35 trials (5058 cefepime patients and 3976 comparators)
  - All cause morality: cefepime (5.63%) and comparator (5.68%)
  
  (Clin Infect Dis 2010; 51: 381)

“Cefepime and Death: Reality to the Rescue”

“With the publication of this mega-meta analysis…Kim and colleagues have now brought clarity and calm to the contentious debate.”

“We are reminded that we have the right to question results that do not necessarily match our clinical experience….”

(Freifeld and Sepkowitz. Clin Infect Dis 2010; 51: 390)
Cephalosporins

- Valuable nontoxic agents in a variety of nosocomial and community-acquired hospital infections
- Caution with CAPES (including ESBL-producers) organisms when using 3rd generation agents
- Cefepime is the only potential monotherapy cephalosporin option in the treatment of ceftriaxone-resistant GNR infection, however, may be associated with increased mortality compared with other agents

Beta-lactamase inhibitor combinations

- Ampicillin-sulbactam (Unasyn®)
- Piperacillin-tazobactam (Zosyn®)
- Ticarcillin-clavulanate (Timentin®)

Beta-lactamase inhibitor combinations: spectrum

- Addition of BLI results in reliable agents vs S. aureus (like nafcillin or cefazolin), H. influenzae (like ceftriaxone), B. fragilis (like metronidazole)
- Zosyn® and Unasyn® are active vs E. faecalis, but not E. faecium; Timentin® has no enterococcal coverage
Beta-lactamase inhibitor combinations: spectrum

- Zosyn® and Timentin® (but not Unasyn®) approximates ceftazidime in gram-negative activity (i.e. HNPEKS plus Pseudomonas)
- Zosyn® and Timentin® have the same weaknesses as ceftazidime vs Citrobacter, Acinetobacter, Enterobacter
- While active in vitro versus many ESBL-producing organisms, BLI combinations are inferior to carbapenems in the treatment of infection
- BLI combinations should not be used as monotherapy in suspected ceftriaxone-resistant gram-negative infections (however, may be reasonable to use in combination with other GNR-active agents)

Fluoroquinolones?

- Five years ago fluoroquinolones were among those agents (cefepime, penems, aminoglycosides) that could logically be used in the treatment of resistant gram negative infection
- The decline in activity vs Pseudomonas, Enterobacter, and E.coli, including ESBL-producers has greatly diminished the role of these agents in the treatment of third generation cephalosporin-resistant gram negative pathogens
Penems: spectrum

- Imipenem, meropenem (and doripenem) are active vs most gram-negative pathogens (including third-generation cephalosporin-resistant and ESBL producers), gram-positive pathogens (including E. faecalis), and anaerobes
- Cannot rely upon ertapenem for ceftriaxone-resistant gram negative infection: little to no Pseudomonas or Acinetobacter coverage, however excellent vs ESBL-producers
- Weaknesses: Stenotrophomonas, Pseudomonas aeruginosa (rapid emergence of resistance over time), methicillin-resistant staphylococci, E. faecium, C. difficile

Penems: Adverse effects

- Hypersensitivity: Early reports of extensive cross-reactivity with penicillin in patients with documented IgE allergy. Most recent data (NEJM 2006; 354: 2835 and Ann Intern Med 2007; 146: 266-269) suggest patients with immediate hypersensitivity to penicillin infrequently have a positive skin test to carbapenems and with a negative skin test to imipenem 0.5 mg/ml (or meropenem 1 mg/ml) can safely receive imipenem/meropenem.
- Seizures: Imipenem (but not meropenem or doripenem) associated with seizures at >50 mg/Kg/D or unadjusted doses in renal failure; also carbapenems decrease serum levels of valproic acid
- Hypotension: Imipenem (but not meropenem) is associated with dose/time of infusion-related hypotension, nausea

Aminoglycosides

- Spectrum: multidrug-resistant gram-negative bacilli (Citrobacter, Enterobacter, Pseudomonas) but rarely used as monotherapy in the treatment of these infections
- More commonly used as a synergistic addition in endocarditis due to viridans streptococci, enterococcus, S. aureus
Aminoglycoside Toxicity

- Dose, time related: toxicity with less than 5 days of therapy is unlikely
- Nephrotoxicity is generally reversible
- Ototoxicity (both cochlear and vestibular) is more often irreversible; elderly are particularly predisposed. Baseline audiometry is mandatory for long-term therapy, especially in elderly
- Drug levels do not reliably predict risk for ototoxicity

Low-Dose Gentamicin Nephrotoxicity

- Antistaphylococcal penicillin or vancomycin plus initial low-dose gentamicin (1 mg/Kg/dose Q 8 H for 4 days) vs daptomycin
- Renal adverse events: daptomycin (7%); vancomycin + gentamicin (19%); antistaphylococcal penicillin + gentamicin (17%)
- Reduction in creatinine clearance: patients receiving gentamicin (22%); patients not receiving gentamicin (8%)
  (Clin Infect Dis 2009; 48: 713-21)

“Back to the Future: Using Aminoglycosides Again and How to Dose Them Optimally”

“Back to the Future”: Key Points

- Toxicity is dose and time dependent
- Patients with normal renal function should receive 5 mg/Kg Q24H
- The breakpoint for gentamicin (tobramycin) susceptibility is 4 mcg/ml, however, the more appropriate upper end breakpoint likely should be 1 mcg/ml
  - “At an MIC of 1.0 mcg/ml, a probability of 90% for a good outcome cannot be attained without accepting a toxicity probability ~60%”

Tigecycline

Tigecycline (Tygacil™) Spectrum of Activity

- Gram negative: Active vs most aerobic gram negative pathogens, including ESBLs and Stenotrophomonas
  - Less active vs Proteus, Morganella, Providencia
  - **No activity vs Pseudomonas
- Gram positive: MRSA, MRSE, enterococcus (including VRE), streptococci
- Anaerobes: both gram positive and gram negative
Tigecycline (Tygacil™)
Pharmacokinetics

- MIC breakpoint is ≤0.5 µg/ml for *S. aureus*, ≤0.25 µg/ml for enterococci, and ≤2 µg/ml for gram-negative bacteria
- $C_{p_{\text{max}}}$ is 0.6-0.9 mcg/ml with 50 mg Q12H IV; OK to use in bacteremic/septic patients?
- $T_{1/2}$ is 42 hrs due to extensive tissue binding

Tigecycline (Tygacil™)

- Adverse events:
  - High rate of upper GI side effects
  - “Tetracycline-like” bone and teeth deposition: contraindicated in pregnancy and children < 8yo
- Development of resistance: reports of emergence while on therapy

Tigecycline in Serious Infection

- FDA Safety Announcement 9/1/10: There is “an increased risk associated with the use of tigecycline compared to that of other drugs used to treat a variety of serious infections.”
Comparision of Tigecycline with Imipenem/Cilastatin for the Treatment of Hospital-Acquired Pneumonia

- Phase 3 mulitcenter RCT comparing tigecycline with imipenem
- Cure rates were 67.9% for tigecycline and 78.2% for imipenem in clinically evaluable patients (62.7% and 67.6% for modified intent to treat population)
  
  (Diagn Microbiol Infect Dis 2010; 68: 140)

Cure Rates: Tigecycline with Imipenem/Cilastatin in Clinically Evaluable Patients

<table>
<thead>
<tr>
<th>Population</th>
<th>Tigecycline</th>
<th>Imipenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA P</td>
<td>35/73 (47.9%)</td>
<td>47/67 (70.1%)</td>
</tr>
<tr>
<td>Non-VA P</td>
<td>147/195 (75.4%)</td>
<td>143/176 (81.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean AUC_{0-24}/MIC ratio</th>
<th>VAP</th>
<th>Non-VA P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>2.644</td>
<td>8.907</td>
</tr>
<tr>
<td>Median</td>
<td>1.730</td>
<td>4.389</td>
</tr>
</tbody>
</table>

(Diagn Microbiol Infect Dis 2010; 68: 140)

Tigecycline: Place in Therapy

- While tigecycline appears to be equal to other traditional therapies in the treatment of less complicated disease states, its broad spectrum of activity vs both resistant gram-positive and gram-negative pathogens suggests it be reserved for the treatment of these more resistant pathogens
- Tigecycline should not be used in septic patients
- Despite the limited clinical experience, the most likely indication will be in the treatment of ESBL-producing Enterobacteriaceae and multi-drug resistant Acinetobacter
- Lack of pseudomonal activity diminishes role in empirical treatment of ceftriaxone-resistant GNR infection
Presumed HAP, VAP or HCAP
Risk* for MDR Pathogen?

YES

NO

1. Antipseudomonal B-lactam*
2. Aminoglycoside (or anti-
pseudomonal quinolone)*
3. Vancomycin (or Linezolid)

Ceftazidime or piperacillin-tazobactam or ceftazidime or carbapenem

*Prior antimicrobial therapy, current hospitalization of 5d or more, high rate of resistance in community or hospital unit, recent hospitalization or nursing home residence, chronic dialysis, home wound care, family member with MDR, immunosuppression

Combination Therapy

- In general, combination therapy has not been found to be superior to beta-lactam monotherapy in the treatment of \textit{P. aeruginosa} bacteremia, however, there are some exceptions
  - Aminoglycoside monotherapy is inferior to combination and should only be used in combination with an antipseudomonal beta-lactam UNLESS the MIC is < 0.25 mcg/ml
  - Neutropenic patients should receive combination therapy
  - In septic patients, a few days of empiric combination therapy and then monotherapy may be the best option

Empiric Monotherapy vs Combination Antibiotic Therapy for Gram-Negative Sepsis

- 760 patients with Gram-negative severe sepsis or septic shock retrospectively analyzed
- 31.3% received inappropriate empiric coverage and mortality significantly higher (51.7%) with inappropriate coverage compared with appropriate (36.4%) coverage
- Mortality with combination (22.2%) was significantly less than with combination (36.0%)


(Antimicrob Agents Chemother 2003; 47: 2756)

(Antimicrob Agents Chemother 2010; 54: 1742)
IMPACT-HAP Study

*Improving Medicine through Pathway Assessment of Critical Therapy in Hospital-Associated Pneumonia*

(Lancet Infect Dis 2011; Online First)

**IMPACT-HAP Study**

- Background: to date, since the publication of the guidelines, several studies have failed to show a benefit of dual Gram-negative therapy over monotherapy
- 303 patients at risk of MDR pneumonia randomized to guideline-compliant vs noncompliant therapy
- Kaplan-Meyer estimate of survival at 28 days was 65% in compliant group vs 79% in noncompliant group

(Lancet Infect Dis 2011; Online First)

**Empirical Treatment of Ceftriaxone/Quinolone-Resistant Gram Negative Infection**

- In order of preference from “clinically stable” to septic shock:
  - Cefepime
  - Carbapenem
  - Piperacillin-tazobactam (or cefepime or ceftazidime) plus tobramycin
  - Carbapenem (*imipenem or meropenem, but not ertapenem*) plus tobramycin
Which of the following agents would be least likely to be active in a patient (receiving ceftriaxone) with gram negative sepsis?

1. Tigecycline
2. Cefepime
3. Piperacillin-tazobactam
4. Ertapenem
5. Imipenem

Options in the Treatment of Multidrug-Resistant Gram-negative Infection

Which of the following agents would be most likely to inhibit multidrug-resistant *P. aeruginosa* and *Acinetobacter*?

1. Tobramycin
2. Ceftaroline
3. Colistin
4. Doripenem
5. Televancin
Role of a 5th Generation Cephalosporin (i.e. Ceftaroline)?

<table>
<thead>
<tr>
<th>Organism</th>
<th>Ceftobiprole or Ceftaroline MIC&lt;sub&gt;90&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA/MRSE</td>
<td>2.0 mcg/ml</td>
</tr>
<tr>
<td>Penicillin-resistant pneumococci</td>
<td>0.25 mcg/ml</td>
</tr>
<tr>
<td>E. faecalis (Ceftobiprole)</td>
<td>4.0 mcg/ml</td>
</tr>
<tr>
<td>E. faecium</td>
<td>&gt;32 mcg/ml</td>
</tr>
<tr>
<td>ESBL+ E. coli</td>
<td>&gt;32 mcg/ml</td>
</tr>
<tr>
<td>ESBL+ Klebsiella</td>
<td>&gt;32 mcg/ml</td>
</tr>
<tr>
<td>Acinetobacter spp</td>
<td>&gt;32 mcg/ml</td>
</tr>
<tr>
<td>Ceftazidime-resistant Pseudomonas aeruginosa</td>
<td>&gt;32 mcg/ml</td>
</tr>
</tbody>
</table>
2011 Update: Ceftobiprole and Ceftaroline

- Ceftobiprole: FDA warning letter in August 2009, followed by complete response letter in December 2009 requesting additional site audits, further studies
- Ceftaroline: FDA approved for skin and soft tissue infection and community acquired pneumonia

Doripenem

- Spectrum essentially that of imipenem or meropenem, however, more active by MIC vs Pseudomonas.
  - MIC doripenem for imipenem-resistant *P. aeruginosa* ranges from 2.0–16mcg/ml
- Despite MIC advantage for some isolates, cross-resistance among carbapenems is the norm
- Renal route of elimination, animal model demonstrates less seizure activity compared with meropenem (and certainly imipenem)
- Indications: complicated intra-abdominal infection and UTI. While not indicated to date, comparable to piperacillin-tazobactam or imipenem for nosocomial pneumonia

Tigecycline
Tigecycline in Treatment of Acinetobacter or Pseudomonas: Maybe……

- Generally active vs Acinetobacter, but never vs Pseudomonas
- Questionable use in sepsis (not well-studied, low serum antibiotic levels, increased mortality in VAP)

Colistin

Colistin: Background

- Structurally and pharmacologically similar to polymixin B
- Bactericidal activity derived from action as cationic detergent
- Binds to phosphate groups in the lipids of the cytoplasmic membrane of GN bacteria
- Renal route of elimination
- Nephrotoxic and neurotoxic
**Colistin in Multidrug-resistant Infection**

<table>
<thead>
<tr>
<th>Study</th>
<th>Clinical Cure or Improvement</th>
<th>Nephrotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reina</td>
<td>8/55 (15%) COL 22/130 (17%) Contr</td>
<td>No toxicity</td>
</tr>
<tr>
<td>Kasiakou</td>
<td>33/50 (66.7%)</td>
<td>8% (4/11 with pre-existing CRF)</td>
</tr>
<tr>
<td>Levin</td>
<td>34/59 (58%)</td>
<td>57%</td>
</tr>
<tr>
<td>Markou</td>
<td>18/24 (73%)</td>
<td>14.3%</td>
</tr>
<tr>
<td>Michalopolous</td>
<td>32/43 (74%)</td>
<td>18.6%</td>
</tr>
</tbody>
</table>

(Am J Health-Syst Pharm 2008; 64: 2462)

**Colistin Nephrotoxicity (Defined by RIFLE Criteria)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk (R)</td>
<td>↑ SCR x 1.5 or GFR ↓ &gt;25%</td>
</tr>
<tr>
<td>Injury (I)</td>
<td>↑ SCR x 2 or GFR ↓ &gt;50%</td>
</tr>
<tr>
<td>Failure (F)</td>
<td>↑ SCR x 3, GFR ↓ &gt;75% or SCR &gt;4</td>
</tr>
<tr>
<td>Loss (L)</td>
<td>Persistent ARF or complete loss of function for &gt;4weeks</td>
</tr>
<tr>
<td>ESKD (E)</td>
<td>ESKD &gt; 3 months</td>
</tr>
</tbody>
</table>

(Clin Infect Dis 2009; 48: 1724)

**Colistin Nephrotoxicity (Defined by RIFLE Criteria)**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>At last dose</th>
<th>1 week after completion</th>
<th>1 month after completion</th>
<th>3 months after completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>No injury</td>
<td>50%</td>
<td>61%</td>
<td>70%</td>
<td>88%</td>
</tr>
<tr>
<td>Risk</td>
<td>21%</td>
<td>19%</td>
<td>20%</td>
<td>12%</td>
</tr>
<tr>
<td>Injury</td>
<td>14%</td>
<td>17%</td>
<td>2%</td>
<td>0</td>
</tr>
<tr>
<td>Failure</td>
<td>6%</td>
<td>3%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Loss</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ESKD</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

(Clin Infect Dis 2009; 48: 1724)
NDM-1 “A Cause for Worldwide Concern”

- New Delhi metallo-beta-lactamase 1
- Pathogens with NDM-1 resistant to all agents except colistin
- Gene encoding this beta-lactamase is easily transferred to other Enterobacteriaceae and also inactivates fluoroquinolones and other agents


Which of the following agents would be most likely to inhibit multidrug-resistant \textit{P. aeruginosa} and \textit{Acinetobacter}?

1. Tobramycin
2. Ceftaroline
3. Colistin
4. Doripenem
5. Televancin

…and the empirical coverage of MRSA?
Which of the following agents would be the least likely choice in the treatment of pneumonia due to MRSA?

1. Trimethoprim-sulfamethoxazole
2. Linezolid
3. Daptomycin
4. Clindamycin
5. Doxycycline

Linezolid vs Vancomycin for MRSA Infection

- Retrospective analysis of 2 prospective, randomized trials of patients with suspected gram-positive pneumonia
- Included 339 with documented S. aureus pneumonia and 160 with MRSA pneumonia
  (Wonderink et al Chest 2003; 124: 1789)
Linezolid vs Vancomycin or Teicoplanin for Nosocomial Pneumonia: Systematic Review and Meta-analysis

- Linezolid and vancomycin equally effective in the treatment of nosocomial pneumonia, including MRSA
- Adverse events
  - Thrombocytopenia (RR 1.93) linezolid>comparators
  - Gastrointestinal (RR 2.02) linezolid>comparators
  - Nephrotoxicity: no difference among groups
  - Mortality: no difference among groups
  (Crit Care Med 2010; 38: 1802)

Role of Linezolid

- Drug of choice for VRE in most patients or those intolerant of vancomycin
- Bone marrow suppression in patients at risk (HIV, malignancy) and receipt of therapy > 10 days)
  Linezolid-resistant VRE and coagulase negative staphyloccal outbreaks have been described
- While some studies suggest improved outcomes over vancomycin in the treatment of MRSA pneumonia, other studies refute this association

High Dose Vancomycin for Methicillin-Resistant S. aureus

- Retrospective review of adult patients with MRSA receiving vancomycin
- Outcomes: clinical response, time to clinical stability, LOS, incidence of nephrotoxicity
  (Arch Intern Med 2006; 166: 2138)
### Univariate Predictors of Response

<table>
<thead>
<tr>
<th>Variable</th>
<th>Responders</th>
<th>Non-responders</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>71.2 (15.6) years</td>
<td>76.0 (15.5) years</td>
<td>0.006</td>
</tr>
<tr>
<td>APACHE II</td>
<td>13.4 (6.7)</td>
<td>19.7 (9.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MIC of 2 mcg/ml**</td>
<td>31/68 (46%)</td>
<td>20/27 (74%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Initial vanc trough ≥ 4 MIC</td>
<td>50/68 (74%)</td>
<td>18/27 (67%)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Arch Intern Med 2006; 166: 2138

### Nephrotoxicity

- Univariate predictors: vancomycin trough, duration of vancomycin therapy, creatinine, concomitant nephrotoxins
- Independent predictor: concomitant nephrotoxins
  - Patients with nephrotoxicity: 10/11 received concomitant aminoglycoside or amphotericin
  - Patients without receipt of concomitant nephrotoxins: nephrotoxicity occurred in 1/44 high-trough and 0/24 low trough patients

Arch Intern Med 2006; 166: 2138

### Vancomycin MIC and Treatment of MRSA Bacteremia

- Independent predictors of mortality
  - Vancomycin MIC of 2 mcg/ml (OR 6.39)
  - Inappropriate empirical therapy (OR 3.62)
  - Increasing age (OR 1.02)
  - Use of corticosteroids (OR 1.85)
  - Ultimately (OR 10.2) or rapidly (OR 1.18) underlying disease
  - Intermediate-risk sources of bacteremia (OR 2.18)
  - Shock (OR 7.38)

(Clin Infect Dis 2008; 46: 193)
2009 Recommendations for Dosing of Vancomycin

- Calculate on total body weight
- Trough serum levels just before dose
- Troughs of 15-20 mcg/ml in “complicated infections, such as bacteremia, endocarditis, osteomyelitis” and troughs >10 mcg/ml “to avoid the development of resistance”

(2009 American Society of Health Systems Pharmacists/Infectious Diseases Society of America, Society of Infectious Diseases Pharmacists Consensus Review)

With increased vancomycin doses (and thus increased serum levels), is there an associated risk for toxicity?

- Increased vancomycin troughs was associated with increased nephroxicity (as defined as increase in serum creatinine of 0.5 or 50% over baseline)

(Clin Infect Dis 2009; 49: 507-14)

- Increased high-frequency hearing loss was observed in patients > 53 yo (however, patients both with and without hearing loss had mean vancomycin troughs of 19 mcg/ml)


Vancomycin Toxicity 2009 State of Affairs:

“Limited data”, “conflicting data characterized by confounding nephrotoxic agents, inconsistent and highly variable definitions of toxicity, and inability to examine the time sequence of events surrounding the changes in renal function secondary to vancomycin exposure.”

(2009 American Society of Health Systems Pharmacists/Infectious Diseases Society of America, Society of Infectious Diseases Pharmacists Consensus Review)
Dosing of Vancomycin in Serious MRSA Infection: Conclusions

- Increasing vancomycin doses and troughs have not been clearly associated with improved outcomes in patients infected with isolates with MIC ≥ 2 mcg/ml. However, an MIC of 2 mcg/ml results in pharmacodynamics, i.e. AUC\textsubscript{24}/MIC, which has been associated with clinical failure. Alternatives to vancomycin should be considered in deep-seated MRSA infection with MIC ≥ 2 mcg/ml.
- Vancomycin monotherapy at usual doses has little to no nephrotoxicity. However, increased doses, i.e. 4 gm/day and receipt of concomitant nephrotoxins, may be associated with increased risk for mild, reversible nephrotoxicity.

Daptomycin (Cubicin®)

- E. faecalis, MSSA, MRSA, MRSE (in vitro only), VRE (in vitro only)
- Intravenous administration 4 mg/Kg/D for skin and soft tissue infection (6 mg/Kg/D for endocarditis and bacteremia) with Clcr > 30 ml/min. Cannot be used in the treatment of pneumonia.
- Toxicity: dose-dependent myopathy at >7 D; observed in 0.2% of patients in clinical trials

(Silverman et al. J Infect Dis 2005; 191: 2149)
Which of the following agents would be the least likely choice in the treatment of pneumonia due to MRSA?

1. Trimethoprim-sulfamethoxazole
2. Linezolid
3. Daptomycin
4. Clindamycin
5. Doxycycline

Dalbavancin, Oritavancin, Telavancin

Dalbavancin vs Vancomycin for Catheter-Related Bacteremia
- Prospective, randomized, controlled multicenter Phase II study
- Dalbavancin 1.0 gm IV and 500 mg one week later
- Vancomycin 1.0gm IV Q 12 H

Dalbavancin vs Vancomycin for Catheter-Related Bacteremia

- Primary outcome: overall response (combined clinical and microbiological response)
  - Dalbavancin: 20/23 (87%; 95% CI 73.2-100)
  - Vancomycin: 14/28 (50%; 95% CI 31.5-68.5)


Oritavancin (Targanta)

- Previously an Eli Lilly drug which was never approved due to infusion-associated thrombophlebitis (now resolved)
- SIMPLIFI “Single or Infrequent Doses for the Treatment of Complicated Skin and Skin Structure Infections”: 82% of patients receiving 1200 mg administered as a single dose and 72% of those administered 200 mg daily for up to one week were cured/improved

Televancin (Vibativ®)

- Vancomycin derivative with in vitro activity 1-2 dilutions more potent than vancomycin
- Dose with normal renal function 10 mg/Kg/24hrs (Half life of 7.5 hrs and post-antibiotic effect of 1-4 hrs)
- Excreted by kidney with dosage adjustment required in renal failure (10 mg/Kg/24hrs with Crcl < 30 ml/min)
  (Clin Infect Dis 2009; 49: 1908)
Televancin

- Approved and non-inferior to vancomycin in skin and soft tissue infection
- As of Dec, 2009, FDA delayed decision regarding an indication for HAP
- Subgroup analysis:
  - Superior (absolute improvement of 10%) to vancomycin in *S. aureus* infection
  - Superior to vancomycin in treatment of *S. aureus* pneumonia with MIC ≥1 mcg/ml

Telavancin Adverse Events

- Altered taste (TEL 22% vs VAN 6%)
- Nausea (TEL 26% vs VAN 14%)
- Vomiting (TEL 13% vs VAN 7%)
- Foamy urine (TEL 12% vs VAN 3%)
- Renal events (TEL 3.4% vs VAN 1.2%)

Dalbavancin, et al: Place in Therapy

- If late phase trials confirm equal to improved efficacy compared with other agents (vancomycin, linezolid, daptomycin) in the treatment of infection, the lipoglycopeptides will compete favorably for the gram-positive infection market
- Once-weekly or single-dose dosing: a major advantage, particularly in the home care therapy (and hospital) setting

- Administration of broad spectrum antibiotic therapy within 1 hr of diagnosis of septic shock
- Reassessment of antibiotic therapy with microbiological and clinical data to narrow coverage... “will reduce the likelihood that the patient will develop superinfection with a pathogenic or resistant organisms, such as *Candida* species, *Clostridium difficile*, or VRE.”
  
  Crit Care Med 2008; 36: 296

The patient spikes a new fever and 3/3 blood cultures are positive for an unidentified yeast………