A 67 year old man with a history of congestive heart failure is admitted to the hospital with a diagnosis of community acquired pneumonia.
Which of the following agents has been least likely associated with microbiological failure in the treatment of pneumococcal pneumonia?

1. Levofloxacin
2. Azithromycin
3. Penicillin
4. Ciprofloxacin
5. Ampicillin

Penicillins for Treatment of Pneumococcal Pneumonia: Does In Vitro Resistance Really Matter?

- Critical review of the published literature
  - There is only a single report of documented microbiologic failure of parenteral penicillin-class antibiotics in the treatment of pneumococcal pneumonia in patients with or without bacteremia
  - There are a number of well-documented reports of treatment failure with quinolones (n≥21) and macrolides (N≥33)

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)

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**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 doxycycline, he experiences respiratory decompensation associated with increased oxygen requirements and a new infiltrate.

Which of the following agents would be least likely to be useful 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. marescens); ceftazidime is the only reliable antipseudomonal 3rd GC
- Fourth generation: cefepime
- Fifth generation?: ceftobiprole (GNRs AND MRSA, enterococcus)

Third-generation Agents (Ceftriaxone): Holes in Gram-negative Spectrum

- Citrobacter
- Acinetobacter
- Pseudomonas (however, ceftazidime strong)
- Enterobacter AND ESBLs
- Stenotrophomonas (and/or Serratia)
Identification of ESBL Producer (CDC)

Gram-negative Activity: Fourth-Generation Agents (Cefepime)

- *H. influenzae*
- *Enterobacter (but not ESBL)*
- *Neisseria*
- *Proteus (and Pseudomonas)*
- *E. coli*
- *Citrobacter*
- *Klebsiella*
- *Serratia*
True or False? Cefepime has been associated with increased mortality when compared with comparator agents.

1. True
2. False

Efficacy and Safety of Cefepime: a Systematic Review and Meta-Analysis

Cefepime Meta-Analysis

- 57 randomized, controlled trials comparing cefepime with a different beta-lactam antibiotic
  - Neutropenic fever
  - Pneumonia
  - UTI/Gynecological
  - Other
- Primary outcome: 30 day all-cause mortality
- Secondary outcomes: clinical failure, microbiological failure, superinfection, adverse events

Cefepime Meta-Analysis

- Cefepime was associated with increased all-cause mortality (RR 1.26 [1.08-1.49]; p=0.005) compared to all other beta-lactams
  - All antibiotic comparators were associated with lower all-cause mortality, with significance shown for piperacillin-tazobactam RR 2.14 [1.17-3.89]; p=0.01
  - Mortality higher in all infection except UTI (no deaths occurred), with significance for febrile neutropenia RR 1.42 [1.09-1.84]; p=0.009
Cefepime Mortality: Proposed Mechanisms

1. “An unrecognized side effect”. Cefepime-associated neurotoxicity, including encephalopathy, status epilepticus, primarily in patients with acute or chronic renal failure
2. “Inadequate antimicrobial efficacy in vivo”. Explained by inoculum effect or other pharmacodynamic considerations.

However……..
Cefepime Secondary Outcomes: Toxicity

1. Adverse events [0.99 [0.94-1.04] and adverse events requiring discontinuation [1.20 [0.94-1.52] were similar in all groups.

2. Neurological complications were the same in both groups [1.16 [0.78-1.13-1.13]. Seizures were reported in one trial (in the imipenem group).

Cefepime Secondary Outcomes: Clinical and Microbiological Efficacy

1. Clinical failure was similar for cefepime compared with the comparator groups [0.98 [0.93-1.03]

2. Microbiological failure was not significantly different for cefepime compared with the comparator groups [0.92 [0.84-1.02]
Cephalosporins

- Valuable nontoxic agents in a variety of nosocomial and community-acquired hospital infections
- Caution with CAPES organisms and 3rd generation agents
- Cefepime is the only 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®)
- Ticarcillin-clavulanate (Timentin®)
- Piperacillin-tazobactam (Zosyn®)
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 activity

Beta-lactamase inhibitor combinations: spectrum

• Zosyn® and Timentin® (but not Unasyn®) approximate ceftazidime in gram-negative activity (i.e. HNPEKS plus Pseudomonas)
• Zosyn® and Timentin® have same weaknesses as ceftazidime vs CAPES organisms. While active in vitro versus many ESBL producing organisms, they are inferior to other drugs
• Neither agent should 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?

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 have greatly diminished the role of these agents in the treatment of third generation cephalosporin-resistant gram negative pathogens
Penems: spectrum

- Imipenem, meropenem and doripenem (*but not ertapenem...which has limited to no activity vs Pseudomonas or Acinetobacter*) active vs most gram-negative pathogens (including third-generation cephalosporin-resistant and ESBL producers), gram-positive pathogens (including E. faecalis), anaerobes
- 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) associated with seizures at >50 mg/Kg/D or unadjusted doses in renal failure
- 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)
- More commonly used as a synergistic addition in endocarditis due to S. viridans, 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
Tigecycline

Tigecycline (Tygacil™)
Spectrum of Activity

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

• MIC breakpoint is $\leq 0.5 \, \mu g/ml$ for *S. aureus*, $\leq 0.25 \, \mu g/ml$ for enterococci, and $\leq 2 \, \mu g/ml$ for gram-negative bacteria
• $C_{p_{\text{max}}}$ is 0.6-0.9 mcg/ml with 50 mg Q12H IV
• $T_{1/2}$ 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: 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

Combination Therapy

• In general, combination therapy has not been found to be superior to beta-lactam monotherapy, 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 (Chamot et al Antimicrob Agents Chemother 2003; 47: 2756)
Empirical Treatment of Ceftriaxone/Quinolone-Resistant Gram Negative Infection

• In order of preference from “clinically stable” to septic shock:
  – Cefepime
  – Carbapenem (but not ertapenem)
  – Piperacillin-tazobactam (or cefepime or ceftazidime) plus fluoroquinolone
  – Piperacillin-tazobactam (or cefepime or ceftazidime) plus tobramycin
  – Carbapenem (but not ertapenem) plus tobramycin

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. Gentamicin
2. Ceftobiprole
3. Colistin
4. Doripenem
5. Ceftazidime

Role of a 5th Generation Cephalosporin (i.e. Ceftobiprole)?
<table>
<thead>
<tr>
<th>Organism</th>
<th>Ceftobiprole 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 pnemococci</td>
<td>0.25 mcg/ml</td>
</tr>
<tr>
<td>E. faecalis</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>
Doripenem

- Spectrum essentially that of imipenem or meropenem, however, more active by MIC vs Pseudomonas.
  - MIC doripenem for imipenem R P. aeruginosa ranges from 2.0->16 mcg/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 in Serious Infection

- 18 patients receiving tigecycline for infection due to multidrug-resistant gram-negative bacilli
  - Resistant to at least 3 classes of antibacterials
  - Susceptibility to tigecycline (< 4.0 mcg/ml “susceptible” and 4.0 mcg/ml “intermediate”)
  - All patients received 100 mg load, followed by 50 mg Q12H

  (Clin Infect Dis 2008; 46: 567)
Results

- 16 of the 18 isolates had MIC testing prior to initiation of tigecycline
  - Of 9 A. baumannii, 5 were intermediate and 4 of these patients died due to infection
  - 8 patients who had persistently positive culture results and 6 had repeat susceptibility testing

(Clin Infect Dis 2008; 46: 567)

Results: tigecycline failures for susceptible isolate

- Persistent *K. pneumoniae* tracheal and pleural isolates, despite 7 days therapy (MIC 1.50 mcg/ml)
- *A. baumannii* mediastinitis and bacteremia with continued positive blood cultures at day 5 (MIC 2 mcg/ml)
- Mediastinitis and aortic pseudoaneurysm due to *K. pneumoniae* with bacteremia at >40 days (MIC 1.0 mcg/ml)
- Retained venous catheter and septic thromobophlebitis with multiple recurrence of *E. coli* bacteremia (MIC <0.75 mcg/ml)

(Clin Infect Dis 2008; 46: 567)
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 P. aeruginosa in Cancer Patients

- Retrospective analysis of 95 patients with multidrug-resistant P. aeruginosa
- Overall clinical response 52% in colistin group versus 31% in control
- Multiple logistic regression: patients treated with colistin 2.9 times (95%CI 1.1-7.6) more likely to experience a clinical response to therapy
- Nephrotoxicity same in each group

(Antimicrob Agents Chemother 2007; 51: 1905)

…and the empirical coverage of MRSA?
**Methicillin-resistant S. aureus**

- Rate of MRSA infection is increasing in the community and in the nosocomial setting
- Nosocomial: 20-50%
- Community: up to 40% in some centers
- Is vancomycin inferior to other agents in the treatment of MRSA infection?
Which of the following agents is the drug of choice for deep-seated infection due to MRSA?

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

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)
Outcome of vancomycin treatment in patients with methicillin-susceptible S. aureus bacteremia

- Retrospective cohort study with propensity score to adjust for confounders and also matched case-control study
  - Cohort mortality: Vanco: 10/27 (37%) and B-lactam 47/267 (18%); p=0.02
  - Case control mortality: Vanco: 10/27 (37%) and B-lactam 6/54 (11%); p<0.01
  (Antimicrob Agent Chemother 2008; 52: 192)
High Dose Vancomycin for Methicillin-Resistant S. aureus

- Retrospective review of adult patients with MRSA receiving vancomycin. “Attending physicians typically requested a pharmacist to dose vancomycin...to achieve a trough of 4-5 times the MIC of the...strain.”

- Outcomes: clinical response, time to clinical stability, LOS, incidence of nephrotoxicity

(Arch Intern Med 2006; 166: 2138)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Responders</th>
<th>Non-responders</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years</td>
<td>71.2 (15.6)</td>
<td>76.0 (15.5)</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 &gt; 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)
Dosing of Vancomycin in Serious MRSA Infection: Conclusions

• Unclear whether increased doses are associated with clearly improved outcomes in patients infected with isolates with MIC 2 mcg/ml and it may be that other risk factors, e.g. virulence factors account for the poor outcome in MRSA pneumonia
• Vancomycin has little to no nephrotoxicity as long as patients are not receiving concomitant nephrotoxins. Increased doses and associated trough levels (i.e. > 15 mcg/ml) are appropriate in patients not receiving nephrotoxins. Patients receiving concomitant nephrotoxins may be better suited receiving alternative primary MRSA therapy (e.g. linezolid, daptomycin)

Linezolid Adverse Events

• Adverse effects: bone marrow suppression, particularly thrombocytopenia
• Mild MAO inhibitor effects and risk for serotonin toxicity
  – FDA postmarketing adverse events: 29 cases of serotonin toxicity in patients receiving concomitant linezolid and other agent known to increase serotonin concentrations (mostly SSRIs); 13 required intervention (Clin Infect Dis 2006; 42: 1578)
  – 72 patients receiving linezolid and SSRl/venlafaxine of which 2 (3%) had high probability of serotonin syndrome. Both patients had rapid reversal of symptoms with discontinuation of serotonergic therapy (Clin Infect Dis 2006; 43: 180)
What is the Role of Linezolid?

- Drug of choice for VRE in most patients
- Bone marrow suppression is real in patients at risk (HIV, malignancy), but less problematic in “normal” patients in the treatment of pneumonia, osteomyelitis, other infections
- Some studies suggest improved outcomes over vancomycin in the treatment of MRSA pneumonia and perhaps skin and soft tissue infection, however this suggestion must be confirmed with prospective clinical trials
- Linezolid-resistant VRE and coagulase negative staphylococci is increasing

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. Inferior to ceftriaxone in CAP??
- Toxicity: dose-dependent myopathy at >7 D; observed in 0.2% of patients in clinical trials
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

(Silverman et al. J Infect Dis 2005; 191: 2149)

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)


Dalbavancin (and other new lipoglycopeptides): 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 dosing: a major advantage, particularly in the home care therapy setting if trials confirm efficacy in the treatment of endocarditis and osteomyelitis

- 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)