**Update on Antimicrobials**

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**Telithromycin**

**Telithromycin is associated with which of the following adverse events?**

1. Exacerbation of myasthenia gravis
2. Visual disturbances
3. Hepatotoxicity
4. Nausea and vomiting
5. All of the above

**Telithromycin (Ketek®) Spectrum**

- A “ketolide” with dose-dependent killing versus PCN-susceptible and resistant and macrolide-susceptible and resistant S. pneumoniae
- Similar to available macrolides versus H. influenzae, M. catarrhalis and atypical bacteria (Mycoplasma, C. pneumoniae, Legionella)

**Telithromycin (Ketek®) Kinetics**

- Half life of 7-11 hrs
- 57% absolute bioavailability with 33% first pass metabolism; can be taken with food; only PO therapy available
- Dose: 800 mg PO QD
- Similar to macrolides, high tissue and cellular concentrations are achieved
- Elimination through multiple pathways, including fecal (7%) and renal (13%)

**Telithromycin (Ketek®) Drug Interactions**

- Competitive inhibitor of CYP3A4 and CYP2D6; known increase in AUC of lovastatin, simvastatin, atorvasatin, midazolam, ergots, ritonavir, metoprolol
- Telithromycin concentrations may be increased with concomitant administration of other CYP3A4 inhibitors such as voriconazole and reduced with inducers such as rifampin, phenytoin, carbamazepine
Telithromycin (Ketek®)
Gastrointestinal Adverse Effects

- Nausea
  - Telithromycin: 7%
  - Comparator: 4.1%
- Vomiting
  - Telithromycin: 2.4%
  - Comparator: 1.4%
- Diarrhea
  - Telithromycin: 10%
  - Comparator: 8%
(Medical Letter 2004; 46: 66-68)

Telithromycin (Ketek®) Other Adverse Events

- Blurred vision, diplopia, difficulty focusing (accommodation) in 1% of patients, 2% in women under 40 yo. Most common after 1st or 2nd dose
- Prolongation of QT (similar to clarithromycin or erythromycin); however not observed in clinical trials
- Aggravation of myasthenia gravis
- Liver failure (Ann Intern Med 2006): 3 patients (1 recovered, 1 required liver transplant, 1 died; the last two patients reported some concomitant alcohol use). Several other cases have been reported since these first reports.
  FDA has determined that additional warnings regarding the risk of liver toxicity are required and the manufacturer has revised the drug labeling to address this safety concern.

Summary: Telithromycin (Ketek®)

- Spectrum of activity, including vs resistant pneumococci, is consistent with that necessary for the treatment of CAP in high risk patients
- May "spare" the use of fluoroquinolones in CAP
- Unclear role in the treatment of other outpatient respiratory infection (As of Feb 2007, FDA has limited indications to just CAP)
- Adverse events (upper GI, liver failure) and drug interactions negatively impact upon potential use

Telithromycin is associated with which of the following adverse events?

1. Exacerbation of myasthenia gravis
2. Visual disturbances
3. Hepatotoxicity
4. Nausea and vomiting
5. All of the above

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. Levofoxacin
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)

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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 American Thoracic Society and Infectious Diseases Society of America for the empirical treatment of hospitalized patients with community acquired pneumonia. New guidelines from combined IDSA/ATS just published in early 2007.
(Clin Infec Dis 2007; 44: S27-72)

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

Seven days into an empirical course of ceftriaxone and doxycycline, he experiences respiratory decompensation associated with increased oxygen requirements and a new infiltrate.
Cephalosporins

• First generation: cefazolin (PEK: Proteus mirabilis, E. coli, Klebsiella)
• Second generation: cefuroxime, cefotetan (cefotetan recently discontinued by manufacturer) (HNPEK: H. influenzae and 1st GC-resistant PEK)
• Third generation: cefotaxime, ceftriaxone, ceftazidime (HNPEKS: S. marsecens); ceftazidime is only reliable antipseudomonal 3rd GC
• Fourth generation: cefepime

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

• Citrobacter
• Acinetobacter
• Pseudomonas (however, ceftazidime strong)
• Enterobacter
• Stenotrophomonas (and/or Serratia)

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

• H. influenzae
• Enterobacter*
• Neisseria
• Proteus (and Pseudomonas*)
• E. coli
• Citrobacter*
• Klebsiella
• Serratia

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

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 (HNPEKS plus Pseudomonas)
- Zosyn® and Timentin® have same weaknesses as ceftazidime vs gram-negative GNRs (CAPES)
- 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?**


- Pseudomonas aeruginosa: ↓ 25.1%
- Escherichia coli: ↓ 6.8%
- Proteus mirabilis: ↓ 11.9%
- Change in percentage of susceptibility was significantly related to increased fluoroquinolone use (P<0.05)
  
  (Clin Infect Dis 2003; 37: 1643)

**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 and meropenem (*but not ertapenem*) active vs most gram-negative (including multidrug-resistant), gram-positive (including E. faecalis), anaerobes
- Weaknesses: Stenotrophomonas, Pseudomonas aeruginosa (development of resistance over time), methicillin-resistant staphylococci, E. faecium, C. difficile

**Penems: Adverse effects**

- Early reports demonstrated extensive cross-reactivity with penicillin in patients with documented IgE allergy. However, most recent data (NEJM 2006; 354: 2835) suggest patients with immediate hypersensitivity to penicillin and a negative skin test to 0.5mg/ml of imipenem can safely receive imipenem.
- Imipenem (but not meropenem) seizures: >50 mg/Kg/D or unadjusted doses in renal failure
- Imipenem: dose/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 (Tygacil™)

Tigecycline

Spectrum of Activity

- Aerobic gram negative
  - Active vs most E. coli (including ESBL), Enterobacter cloacae, Citrobacter freundii, Klebsiella spp, Acinetobacter, Serratia, Stenotrophomonas
  - Less active vs Proteus, Morganella, Providencia spp and essentially inactive vs Pseudomonas

- Aerobic gram-positive
  - Approved: Enterococcus faecalis, S. aureus (MSSA and MRSA), S. pyogenes, S. anginosis
  - Active in vitro but not clinically proven: Enterococcus faecium (including VRE), Listeria, S. epidermidis (MSSE and MRSE)

- Anaerobic
  - Bacteroides fragilis, other Bacteroides, C. perfringens, Prevotella spp.

- Other microorganisms
  - Active in vitro but not clinically proven: Mycobacterium abscessus, M. cheloneae, M. fortuitum
Tigecycline (Tygacil™)

- Adverse events: high rate of upper GI side effects, “tetracycline-like” (bone and teeth deposition): contraindicated in pregnancy and children < 8yo, superinfection, antibiotic associated colitis
- Development of resistance: unknown, but history of tetracycline resistance is concerning

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
- 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

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

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4. Ertapenem
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…and the empirical coverage of resistant gram positive pathogens (MRSA, VRE)?

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 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 for MRSA Infection

- “Wunderlink and coworkers combined the databases of two publications…a procedure not too attractive in scientific research.”
- “Interpretation of the study…would be deceiving if it leads to an empiric treatment of nosocomial pneumonia with linezolid for 3 reasons:”
  - Treatment of large numbers of patients who don’t need the drug
  - Development of linezolid resistance
  - Increased cost (Bauer. Chest 2003; 124: 1632)

Etiology of Vancomycin “Failure” in MRSA Pneumonia

- Slow bacterial killing compared to beta-lactams (maybe, but hard to prove with currently available agents since organism is methicillin-resistant)
- Insufficient serum levels in deep seated infection, particularly pneumonia, however, vancomycin serum levels have not been clearly associated with any outcome, therapeutic or toxic. Pharmacodynamic studies suggest that low vancomycin concentrations in lung epithelial lining fluid (result of inability of vancomycin to passively diffuse through plasmatic membrane of eukaryotic cells) are etiology for poor response in pneumonia. Suggest troughs of 15-20 mcg/ml in patients with pneumonia, meningitis, osteomyelitis.
- Upregulation of virulence factors in organisms with “higher” MIC (early studies suggest strongly possible)

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)
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 (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>
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<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>

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: nephrotoxiciti occurred in 1/44 high-trough and 0/24 low trough patients

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 Mitochondrial Toxicity

- Lactic acidosis (NEJM 2003; 348: 86)
- Optic neuropathy (Clin Infect Dis 2003; 37: 1389)
- Patient with optic neuropathy, encephalopathy, skeletal myopathy, lactic acidosis, renal failure after 4 months of linezolid. Biopsy of muscle, liver, kidney all demonstrated decreased mitochondrial chain enzyme activity and associated protein synthesis (Clin Infect Dis 2006; 42: 1111)

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); 15 required intervention (Clin Infect Dis 2006; 42: 1278)
  - 72 patients receiving linezolid and SSRI/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)

Linezolid-Mitochondrial Toxicity

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- Optic neuropathy (Clin Infect Dis 2003; 37: 1389)
- Patient with optic neuropathy, encephalopathy, skeletal myopathy, lactic acidosis, renal failure after 4 months of linezolid. Biopsy of muscle, liver, kidney all demonstrated decreased mitochondrial chain enzyme activity and associated protein synthesis (Clin Infect Dis 2006; 42: 1111)

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 CrCl > 30 ml/min. Inferior to ceftriaxone in CAP??
- Toxicity: dose-dependent myopathy at >7 D; observed in 0.2% of patients in clinical trials

#### 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 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


#### 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
Which of the following agents has been associated with a more virulent form of antibiotic associated colitis?

1. Fluoroquinolones
2. Ceftriaxone
3. Clindamycin
4. Piperacillin-tazobactam
5. Metronidazole

Clostridium difficile

- Causes: toxins A and B
- Risks: Age, hospitalization, antibiotic exposure
- During last few years, more frequent, more severe disease which is more refractory to standard treatment
  
  (Clin Infect Dis 2006; 43: 428)

Epidemic, Toxin Gene-Variant Strain of Clostridium difficile

- Background: recent reports suggest rate and severity of C. difficile disease is increasing
- Total of 187 C. difficile isolates between 2000 and 2003 characterized and compared with a database of >6000 isolates from prior to 2001
  

Levofloxacin MIC: BI/NAP1 vs Non-BI/NAP1 isolates

Which of the following agents has been associated with a more virulent form of antibiotic associated colitis?

1. Fluoroquinolones
2. Ceftriaxone
3. Clindamycin
4. Piperacillin-tazobactam
5. Metronidazole

Which of the following agents would be the best choice in the treatment of fungemia due to C. glabrata?

1. Anidulafungin
2. Caspofungin
3. Micafungin
4. Any echinocandin
5. Fluconazole

Anidulafungin, Caspofungin or Micafungin?

- Spectrum of activity: identical for all three agents (anidulafungin, caspofungin, micafungin)
  - Highly active (and cidal) : C. albicans, C. glabrata, C. tropicalis
  - Very active: C. parapsilosis, Aspergillus
  - Some activity: Coccidiodes, Blastomyces, Scedosporium, Histoplasma

<table>
<thead>
<tr>
<th></th>
<th>Caspofungin</th>
<th>Micafungin</th>
<th>Anidulafungin</th>
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</thead>
<tbody>
<tr>
<td>Dose (invasive candidiasis)</td>
<td>70 mg load then 50 mg Q 24 H</td>
<td>50-150 mg Q 24 H (likely then 100 mg/D)</td>
<td>200 mg load then 100 mg/D</td>
</tr>
<tr>
<td>Protein binding</td>
<td>96%</td>
<td>99.8%</td>
<td>84%</td>
</tr>
<tr>
<td>Renal/Hepatic Dosing</td>
<td>Hepatic: DECREASE</td>
<td>No Change</td>
<td>No Change</td>
</tr>
<tr>
<td>CSF levels</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Urinary levels</td>
<td>1%</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Significant Interactions</td>
<td>Enzyme inducers</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Adverse reactions

- “The adverse events and toxic effects of the echinocandins have been few.”
  - Histamine release is common with basic polypeptide compounds
  - LFT abnormalities with concomitant caspofungin + cyclosporine (but not micafungin or anidulafungin). Subsequent retrospective analyses suggest that caspofungin can be safely co-administered with cyclosporine

Place in Therapy

- Caspofungin (and the other echinocandins) are drugs of choice in the treatment of most nonalbicans Candida
- They can be used synergistically with voriconazole in the treatment of Aspergillus
- Micafungin (and anidulafungin) are “me too” antifungals to caspofungin. Acquisition cost will dictate choice of echinocandin

Which of the following agents would be the best choice in the treatment of fungemia due to C. glabrata?

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