Rational Use of Antimicrobials in Hospital Medicine

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A 77 year old man with a history of congestive heart failure is admitted to the hospital with a diagnosis of community-acquired pneumonia.

Which choice is most appropriate in the treatment of CAP in this patient?

1. Moxifloxacin
2. Ceftriaxone + azithromycin
3. Piperacillin-tazobactam + azithromycin
4. Vancomycin + aztreonam

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 macrolide or doxycycline

ICU
1. An IV beta-lactam (ceftriaxone, cefotaxime, ampicillin-sulbactam) plus an IV fluoroquinolone (levofloxacin, moxifloxacin) or IV azithromycin
He reports a history of a penicillin allergy.

Which choice is most appropriate in the treatment of CAP in this patient?
1. Moxifloxacin
2. Ceftriaxone + azithromycin
3. Piperacillin-tazobactam + azithromycin
4. Vancomycin + aztreonam

The cross-reactivity between penicillin and ceftriaxone is:
1. 30%
2. 20%
3. 10%
4. 5%
5. <5%

Cross-reactivity: Penicillin and Cephalosporins
- Patients: 128 consecutive patients who sustained anaphylactic shock (n=81) or urticaria (n=47) and had positive results with penicillin skin tests
- All patients were skin tested with cephalothin, cefamandole, cefuroxime, ceftazidime, ceftriaxone, and cefotaxime
- Patients with negative results for the last 4 cephalosporins were challenged with cefuroxime axetil and ceftriaxone
  (Ann Intern Med 2004; 141: 16-22)
Cross-reactivity: Penicillin and Cephalosporins

- 14 patients (10.9%) had positive results on skin tests for cephalosporins
- Skin test results for the minor determinant mixture were positive in 10/14 patients (71.4%) with cross-reactivity and 44/114 (38.6%) without cross-reactivity
- All 101 patients with negative results on skin tests for the cephalosporins tolerated cefuroxime axetil and ceftriaxone (tolerability rate, 100%)

(Ann Intern Med 2004; 141: 16-22)

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 the best choice in a patient (receiving ceftriaxone) with gram negative bacteremia?

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

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

- Citrobacter
- Acinetobacter
- Pseudomonas (however, ceftazidime strong)
- Enterobacter AND ESBLs
- Stenotrophomonas (and/or Serratia)
Which of the following statements is correct regarding ESBL-producers?

1. Usual in vitro susceptibility testing cannot reliably identify ESBL
2. Concomitant aminoglycoside, fluoroquinolone, TMP-SMX, ertapenem resistance is common
3. Carbapenems and BLI combinations are drugs of choice

Extended Spectrum Beta-Lactamase (ESBL): Key Points

• ß-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
• Carbapenems have been associated with the most favorable outcomes in the treatment of serious infection associated with ESBL producers
• 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)
**Susceptibility ESBL Isolates**

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>E. coli</th>
<th>K. pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ertapenem</td>
<td>83.8%</td>
<td>76.4%</td>
</tr>
<tr>
<td>Meropenem</td>
<td>100%</td>
<td>99.3%</td>
</tr>
<tr>
<td>Imipenem</td>
<td>100%</td>
<td>97.9%</td>
</tr>
</tbody>
</table>

Antimicrob Agents Chemother 2012; 56: 2888

**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

**Survival: Carbapenems vs Cefepime in the Treatment of ESBL Infection**

(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

“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)

Cefepime Seizures

- 59 cases of nonconvulsive status epilepticus through Feb 2012
  - Concomitant renal dysfunction: 58/59
  - Reduction of dose with renal dysfunction: 3/59
  - Status resolved in 43/59
  - FDA: “health care professionals should adjust the dosage in patients with Clcr ≤ 60”
    (FDA 6/26/12)

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 (including 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 not as established as carbapenems in the treatment of ESBL
- 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 have greatly diminished the role of these agents in the treatment of third generation cephalosporin-resistant gram negative pathogens

**Penems: spectrum**

- Imipenem, meropenem 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 and moderate to strong coverage 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. More recent data (NEJM 2006; 354: 2835 and Ann Intern Med 2007; 146: 266-269) suggest patients with immediate hypersensitivity to penicillin infrequently with 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
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

Tigecycline (Tygaci™) 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 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.”

Comparison of Tigecycline with Imipenem/Cilastatin for the Treatment of Hospital-Acquired Pneumonia

• Phase 3 multicenter 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>VAP</td>
<td>35/73 (47.9%)</td>
<td>47/67 (70.1%)</td>
</tr>
<tr>
<td>Non-VAP</td>
<td>147/195 (75.4%)</td>
<td>143/176 (81.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean $\frac{AUC_{0-24}}{MIC}$ ratio</th>
<th>Tigecycline</th>
<th>Imipenem</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 and Association with Excess Death

- Meta-analysis with 10 published and 3 unpublished studies (N=7434)
- Across randomized, controlled trials, tigecycline was associated with increased mortality and noncure rates
- Impact remained significant for:
  - Trials of approved indications
  - Trials performed before 2005
  (Clin Infect Dis 2012; 54: 1699)

Two drugs are superior to one in the treatment of serious gram negative infection.

1. True
2. False

Combination Therapy

- In general, combination therapy has not been found to be superior to beta-lactam monotherapy in the treatment of *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
  - 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 2010; 54: 1742)
Empirical Treatment of Ceftriaxone/Quinolone-Resistant Gram Negative Infection

- In order of preference from “clinically stable” (Top) to septic shock (Bottom):
  - Cefepime
  - Carbapenem
  - Piperacillin-tazobactam (or cefepime or ceftazidime) plus tobramycin
  - Carbapenem *(imipenem or meropenem, but not ertapenem)* plus tobramycin

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>
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<th>Organism</th>
<th>Ceftobiprole or Ceftaroline MIC&lt;sub&gt;90&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<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>
… 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-sulfa
2. Linezolid
3. Daptomycin
4. 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)
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)

Linezolid vs Vancomycin for MRSA Nosocomial Pneumonia

- RCT of patients with HAP or HCAP MRSA pneumonia
- Vancomycin appropriately dosed via serum levels
- Primary outcome: Clinical outcome at end of study in evaluable per-protocol patients
- Secondary outcomes: clinical outcome in modified intent-to-treat patients, microbiologic response, survival, safety

Linezolid vs Vancomycin for MRSA Nosocomial Pneumonia

- N=1184 patients of which 448 (linezolid n=224; vancomycin n=176) treated per protocol
- Clinical success at end of study
  - Linezolid 95/165 (57.6%)
  - Vancomycin 81/174 (46.6%) (p=0.042)
- All cause 60 Day Mortality
  - Linezolid 15.7%
  - Vancomycin 17.0%

Linezolid for Chronic XDR-TB: A reminder regarding drug safety

**Clinical Significance of Vancomycin MIC**

- Systematic review and meta-analysis performed via Cochrane guidelines
- Vancomycin MIC significantly associated with increased mortality in MRSA bloodstream infection
- MIC ≥ 2mcg/ml by Etest associated with increased mortality
  

**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)*

**Vancomycin Nephrotoxicity**

“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)*

**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
Daptomycin vs Vancomycin in MRSA Isolates with MIC> 1 µg/ml

- Retrospective case-control study of MRSA bloodstream infection with MIC >1 µg/ml
- 118 vancomycin-treated versus 59 daptomycin-treated subjects
- Most with MIC =1.5 µg/ml by E-test
- Clinical failure defined compositely as mortality, microbiologic failure, and/or recurrence of infection

(Clin Infect Dis 2012; 54: 51)

Daptomycin vs Vancomycin in MRSA Isolates with MIC> 1 µg/ml

- Clinical failure:
  Vancomycin 31%
  Daptomycin 17% (p=0.084)
- Independent risk factors for clinical failure:
  Acute renal failure: OR 3.91 (CI 1.05-14.56)
  Vancomycin: OR 3.13 (CI 1.00-9.76)
- 60 day mortality: significantly greater with vancomycin (p=0.022)

(Clin Infect Dis 2012; 54: 51)

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2013

- 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 2013; 41: 580)
Which is most correct regarding the use of procalcitonin?

1. Associated with decreased use of unnecessary antibiotics
2. Associated with decreased mortality
3. Both #1 and #2

What is the role of procalcitonin in the diagnosis of pneumonia?

• Background:
  – Inflammatory markers, such as ESR, C-reactive protein lack specificity in determining the etiology of inflammatory states, specifically infection
  – Procalcitonin is a peptide precursor of the hormone calcitonin
  – Elevated in bacterial, fungal, parasitic infection
  – Not elevated in viral, non-infectious inflammation
  – May serve as a biomarker to guide use of antimicrobials

Use of Procalcitonin (PCT) and Antimicrobial Usage

Depends upon use in primary care vs ED vs ICU/inpatient, however, general recommendation for antibiotics is:

- PCT ≤ 0.1 µg/L: Strongly discourage
- PCT 0.1-0.25 µg/L: Discourage
- PCT 0.25-0.5 µg/L: Encourage
- PCT >0.5 (>1.0 in ICU): Strongly encourage

Procalcitonin (PCT): Established Benefits

• No significant difference in mortality between PCT-treated and controls
• Consistent, significant reduction in antibiotic usage (~20-40%)

Kopterides et al. Crit Care Med 2010; 38: 2229
Schuetz et al. Arch Intern Med 2011; 171: 1322