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 (“in revision” as of Feb 2015)

**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
And….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
How Common is Penicillin Allergy?

- 500 patients with medical record history of “penicillin allergy” skin tested with penicilloyl-polylysine (Pre-Pen®) and fresh penicillin G
- Negative tests followed by oral amoxicillin challenge
- Four patients reacted with any positive skin tests and another 4 had “significant reactions” to the amoxicillin

(J All Clin Immunol 2013 Feb Abstract 829)

The cross-reactivity between penicillin and ceftriaxone is:

1. 15%
2. 10%
3. 5%
4. 1-5%
5. <1%
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, ceptriaxone, and cefotaxime
- Patients with negative results for the last 4 cephalosporins were challenged with cefuroxime axetil and ceptriaxone
  (Ann Intern Med 2004; 141: 16-22)

Cross-reactivity: Penicillin and Cephalosporins

- 14 patients (10.9%) had positive results on skin tests for cephalosporins
- All 101 patients with negative results on skin tests for the cephalosporins tolerated cefuroxime axetil and ceptriaxone (tolerability rate, 100%)
  (Ann Intern Med 2004; 141: 16-22)
Antibacterial choice with “penicillin allergy” (*J Allerg Clin Immunol* 2014; 790)

<table>
<thead>
<tr>
<th>Penicillin allergy</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Vancomycin (21.2%)</td>
<td>1. Cefazolin</td>
</tr>
<tr>
<td>2. Ciprofloxacin (21.1%)</td>
<td>2. Ceftriaxone</td>
</tr>
<tr>
<td>3. Clindamycin (24.4%)</td>
<td>3. Vancomycin (12.4%)</td>
</tr>
<tr>
<td>5. Metronidazole</td>
<td>5. Ciprofloxacin (13.0%)</td>
</tr>
<tr>
<td>6. Cefazolin</td>
<td>6. Piperacillin</td>
</tr>
<tr>
<td>7. Gentamicin</td>
<td>7. Azithromycin</td>
</tr>
<tr>
<td>8. Azithromycin</td>
<td>8. Ampicillin</td>
</tr>
<tr>
<td>10. Ceftazidime</td>
<td>10. Ceftazidime (4.5%)</td>
</tr>
</tbody>
</table>

Penicillin and cephalosporin allergy: 5 educational messages

1. Penicillin allergy is overdiagnosed
2. Penicillin allergy is not due to reactions to the β-lactam ring.
3. Predictive value of penicillin skin testing may be enhanced by using minor determinants mixture (but incredibly complicated to make)
4. The cross-reactivity between penicillin and cephalosporins is 1-2.5%
5. Cephalosporin allergy does not cross all generations
   (*Ann Allerg Asthma Immunol* 2014; 112: 404)
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)
- *ESBLs AND Enterobacter*
- *Stenotrophomonas* (and/or Serratia)

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 appear to be susceptible to extended-spectrum cephalosporins, however, 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 used to be historically difficult

(Ann Pharmacother 2007; 41: 1427)

Extended Spectrum Beta-Lactamase (ESBL): Key Points

- Imipenem and meropenem are the most reliable agents in the treatment of ESBL
- While active in vitro, ertapenem, tigecycline, colistin, cefepime, piperacillin-tazobactam have limited clinical experience but are potential options

(Ann Pharmacother 2007; 41: 1427)
Susceptibility ESBL Isolates

<table>
<thead>
<tr>
<th></th>
<th>E. coli</th>
<th>K. pneumoniae</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)

- *Enterobacter*
- *Pseudomonas*
- *E. coli (but MIC should be ≤ 2 mcg/ml for ESBL-producing isolates)*
- *Citrobacter* *
- *Klebsiella (but but MIC should be ≤ 2 mcg/ml for ESBL-producing isolates)*

(J Antimicrob Chemother 2014; 69: 871)
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: gram-negative 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
- BLI combinations are not as established as carbapenems in the treatment of ESBL. If MIC to piperacillin-tazobactam is ≤ 16 mcg/ml, can potentially use as a carbapenem-sparing agent
- BLI combinations should not be used as monotherapy in suspected severe 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
**Carbapenems: Adverse effects**

- Hypersensitivity in penicillin-allergic patients:
  - Immediate hypersensitivity to carbapenems occurs very infrequently
  - Patients with a negative skin test to imipenem 0.5 mg/ml (or meropenem 1 mg/ml) can safely receive imipenem/meropenem.
    (NEJM 2006; 354: 2835; Ann Intern Med 2007; 146: 266)
- Seizures:
  - Imipenem (but not meropenem or doripenem) is associated with seizures at >50 mg/Kg/D or with unadjusted doses in renal failure
  - 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
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

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; 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.”

Comparision 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>

Mean AUC$_{0-24}$/MIC ratio

<table>
<thead>
<tr>
<th></th>
<th>VAP</th>
<th>Non-VAP</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>

( Диаг Микробиол Инфекц Дис 2010; 68: 140)

Tigecycline and 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
  (Clin Infect Dis 2012; 54: 1699)
Tigecycline FDA Warning
(Oct 2013)

• Boxed warning: increased all-cause mortality; tigecycline should be reserved for use in situations when alternative treatments are not suitable
• Addition of limitations of use: not indicated for the treatment of diabetic foot infection or ventilator-associated pneumonia

Blood cultures return positive for *Pseudomonas aeruginosa*
Two drugs are superior to one in the treatment of serious Pseudomonal 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 monotherapy (36.0%) (Antimicrob Agents Chemother 2010; 54: 1742)

Single-Drug or Combination: *P. aeruginosa* Bacteremia

- Posthoc analysis of patients with PA bacteremia from a prospective cohort
  - Overall 30 day mortality was 30% and did not differ between monotherapy and combination therapy
  - Authors’ conclusions: “This information could help prevent the overuse of antibiotics….” (Clin Infect Dis 2013; 57: 208)
Empirical Treatment of Ceftriaxone/Quinolone-Resistant Gram Negative Infection

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

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. Minocycline
Role of a 5\textsuperscript{th} Generation Cephalosporin (i.e. Ceftaroline)?

<table>
<thead>
<tr>
<th>Organism</th>
<th>Ceftobiprole or Ceftaroline MIC\textsubscript{90}</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>Organism</td>
<td>Ceftobiprole or Ceftaroline MIC&lt;sub&gt;90&lt;/sub&gt;</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>--------------------------------------------</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-resistant *P. aeruginosa* ranges from 2.0->16mcg/ml
- Despite MIC advantage for some isolates, cross-resistance among carbapenems is the norm
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)
Extended Infusions for resistant Pseudomonas?

Extended-infusion antibacterials and treatment of resistant *Pseudomonas*:

- B-lactams demonstrate time-dependent killing, thus if T>MIC is maximized, can still use for “resistant” isolates.
- Optimal outcomes: % of the dosing interval in which the free (unbound) drug concentration remains above the MIC:
  - Cephalosporins: 60-70%
  - Penicillins: 50%
  - Carbapenems: 40%
Extended-infusion antibacterial regimens

- Cefepime 2 gm over 4 hours Q 8 H
- Meropenem 2 gm over 3 hours Q 6 H
- Piperacillin-tazobactam 3.375gm over 4 hours Q 6 H
- Continuous infusions (but pharmaceutical stability issues for some agents and uses up necessary intravenous access)

Piperacillin-tazobactam for Pseudomonas aeruginosa infection: clinical implications of an extended-infusion dosing strategy  Lodise et al CID 2007; 44: 357-363

Probability of achieving piperacillin concentration in excess of the MIC for 50% of the dosing interval
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></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>37%</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;4 weeks</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>59%</td>
<td>61%</td>
<td>70%</td>
<td>88%</td>
</tr>
<tr>
<td>Risk</td>
<td>21%</td>
<td>19%</td>
<td>28%</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)

Intravenous Minocycline and Acinetobacter

- Primarily bacteriostatic, but bactericidal in combination with carbapenems or colistin
- Published experience to date is a total of 23 cases of MDR Acinetobacter pneumonia most of which were treated successfully
- More limited experience in the treatment of SSTI and bacteremia

[Clin Infect Dis 2014; 59 (Suppl 6): S374]
Ceftolozane/tazobactam (Zerbaxa®)?

- Approved for complicated UTIs and intra-abdominal infection
- Current investigation for ventilator-associated pneumonia
- Unlike piperacillin-tazobactam, must add metronidazole for intra-abdominal infection

Ceftolozane/tazobactam: in vitro activity vs MDR Pseudomonas

<table>
<thead>
<tr>
<th></th>
<th>MIC 50</th>
<th>MIC 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftolozane/tazobactam</td>
<td>4 mcg/ml</td>
<td>&gt;32 mcg/ml</td>
</tr>
<tr>
<td>Cefepime</td>
<td>16 mcg/ml</td>
<td>&gt;16 mcg/ml</td>
</tr>
<tr>
<td>Meropenem</td>
<td>8 mcg/ml</td>
<td>&gt;8 mcg/ml</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>&gt;64 mcg/ml</td>
<td>&gt;64 mcg/ml</td>
</tr>
<tr>
<td>Amikacin</td>
<td>16 mcg/ml</td>
<td>&gt;32 mcg/ml</td>
</tr>
<tr>
<td>Colistin</td>
<td>1 mcg/ml</td>
<td>2 mcg/ml</td>
</tr>
</tbody>
</table>

Ceftolozane/tazobactam: in vitro activity vs MDR non-pseudomonal GNR

<table>
<thead>
<tr>
<th></th>
<th>MIC50</th>
<th>MIC90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftolozane/</td>
<td>2 mcg/ml</td>
<td>&gt; 32 mcg/ml</td>
</tr>
<tr>
<td>tazobactam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>&gt; 16 mcg/ml</td>
<td>&gt; 16 mcg/ml</td>
</tr>
<tr>
<td>Meropenem</td>
<td>≤ 0.06 mcg/ml</td>
<td>8 mcg/ml</td>
</tr>
<tr>
<td>Piperacillin-</td>
<td>32 mcg/ml</td>
<td>≥ 64 mcg/ml</td>
</tr>
<tr>
<td>tazobactam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&gt; 8 mcg/ml</td>
<td>&gt; 8 mcg/ml</td>
</tr>
<tr>
<td>Colistin</td>
<td>0.5 mcg/ml</td>
<td>&gt; 4 mcg/ml</td>
</tr>
</tbody>
</table>


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

- 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.”
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
Antibiotic Overuse and C. difficile: A Teachable Moment

A woman in her 80’s with H/O diabetes and arm laceration presented to ED with suspected necrotizing fasciitis. Clindamycin, imipenem, and vancomycin were started and surgical exploration and debridement confirmed the diagnosis. Several operative cultures were positive for group A streptococcus.

[JAMA Internal Med (published on line June 16, 2014: E1-2)]

Antibiotic Overuse and C. difficile: A Teachable Moment

She underwent 2 additional debridements and treatment with imipenem, clindamycin, and vancomycin continued for 21 days. One day after antibiotics were stopped, the patient developed fever and profuse diarrhea and stool testing revealed C. difficile. She ultimately became hypotensive, acidotic and abdominal ultrasound revealed toxic megacolon. Colectomy was recommended, however, her family declined, and the patient soon died.

[JAMA Internal Med (published on line June 16, 2014: E1-2)]