Antibiotics 201: Gram-negatives

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Disclosures

No potential conflicts of interest.
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 + doxycycline
IDSA/ATS Recommendations*
(*Projected Publication Summer 2018)

Non-ICU Ward Admission

PO/IV respiratory fluoroquinolone (levofloxacin (750mg), moxifloxacin, gemifloxacin) OR IV beta-lactam (ceftriaxone, cefotaxime, ampicillin) plus macrolide or doxycycline

ICU Admission

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 + doxycycline

Penicillin allergy update

- Often diagnosed early in life and usually associated with viral rashes in those children who received penicillins for a viral syndrome
- Most patients “allergic” to penicillin are not
- 10% of U.S. patients carry a label of penicillin allergy
- Less than 10% of those with the label who are tested in speciality clinics are found to be at true risk for acute allergy to penicillin

(JAMA 2017; 318: 1: 82-3)
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

(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, 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
• 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)
Impact of Reported Beta-Lactam Allergy on Inpatient Outcomes

– Using a prospective cohort design, 95/507 (19%) of patients reported beta-lactam allergy
– For 72/95 (76%), beta-lactam was preferred therapy
– 25 of the 72 did not receive beta-lactams because of their “allergy”
– Adverse events were 3 times higher in patients who did not receive preferred beta-lactams vs those that did.

(Clin Infect Dis 2016; 63: 904)

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 HAP 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)
  (Clin Infect Dis 2017: 64: 972-80)

Extended Spectrum Beta-Lactamase (ESBL): Key Points

- Imipenem and meropenem are most consistently associated with favorable outcomes in serious ESBL infection
- Ertapenem, tigecycline, colistin, cefepime, piperacillin-tazobactam have been associated with conflicting results. Newer agents are now available.
- Carbapenem overuse has resulted in emergence of carbapenem-resistant Enterobacteriaceae
  (Clin Infect Dis 2017: 64: 972-80)
Gram-negative Activity: Cefepime
(Expansion of gram negative spectrum over ceftriaxone)

- *Enterobacter*
- *Pseudomonas*
- *E. coli (including ESBL-producing isolates)*
- *Citrobacter*
- *Klebsiella (including 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 for “susceptible” ESBL bacteria

• Propensity score-matched cohort study
• When compared with carbapenem therapy, there was a trend toward increased mortality in the cefepime-treated group: (HR, 2.87, 95% CI, 0.88-9.41)
  (Wang et al. Open Forum Infect Dis 2016 Sep; 3(3): ofw132)

Cefepime Neurotoxicity

• 198 cases of neurotoxicity (as of July 2016)
  – Mean age 67 years old
  – Decreased consciousness (80%), disorientation/agitation (47%), myoclonus (40%)
  – Nonconvulsive status epilepticus (31%); convulsive status epilepticus (11%)
  – Concomitant renal dysfunction: 87%
  – Reduction of dose with renal dysfunction: 3/59
  (Appa et al. Open Forum Infect Dis 2017 Fall; 4(4): ofx170)
“First generation” 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

- Piperacillin-tazobactam approximates ceftazidime in gram-negative activity (including Pseudomonas)
- Piperacillin-tazobactam has similar weaknesses as ceftazidime vs Citrobacter, Acinetobacter, Enterobacter
- As with cefepime, BLI combinations are not as consistently effective as imipenem/meropenem in the treatment of ESBL-producing organisms
- BLI combinations should not be used as monotherapy in suspected or confirmed severe ceftriaxone-resistant gram-negative infections
- Piperacillin-tazobactam may have a role alone or in combination therapy in less ill patients

Carbapenems vs BLI Combinations in Treatment of ESBL

N=14 (13/14 studies with extractable data regarding empirical therapy and 7/14 studies regarding definitive therapy)

- Mortality:
  - **Empirical**: Carbapenem 22.1%; BLI combo 20.5%
  - **Definitive**: Carbapenem 15.2%; BLIcombo 16.2%

  (Muhammed et al. Open Forum Infect Dis 4 (2), ofx099, 2017 May 16)
**Piperacillin and Vancomycin nephrotoxicity**

- Vancomycin is associated with mild, reversible nephrotoxicity, particularly when receiving other known nephrotoxins (aminoglycosides)
- Many well-controlled retrospective studies confirm that concomitant receipt of piperacillin-tazobactam is associated with a significant increase in nephrotoxicity
  
  (Clin Infect Dis 2017; 65: 2137-43)

**Risk of AKI with vancomycin in combination with piperacillin-tazobactam or cefepime**

- Rate of AKI was significantly higher with V+PT (81/279; 29%) vs V+C (31/279; 11%)
- Multivariate analysis: V+PT an independent predictor for AKI (Hazard ratio=4.27; 95%CI 2.73-6.68)
- Median onset of AKI was more rapid with V+PT (3 days) compared to V+C (5 days)
  
  (Clin Infect Dis 2017; 64: 116-23)
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 monotherapy treatment of third generation cephalosporin-resistant gram negative pathogens.

Carbapenems: gram negative spectrum

- Imipenem, meropenem are active vs most gram-negative pathogens (including third-generation cephalosporin-resistant and ESBL producers).
- **Cannot rely upon ertapenem** for ceftriaxone-resistant gram negative infection: little to no Pseudomonas or Acinetobacter coverage and less predictable activity vs ESBL (compared with other carbapenems).
- Weaknesses: Stenotrophomonas, Pseudomonas aeruginosa (rapid emergence of resistance over time). Carbapenem-resistant Enterobacteriaceae (CRE) are increasingly more common.
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

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: includes ceftriaxone-resistant gram-negative bacilli (Citrobacter, Enterobacter, Pseudomonas) but less effective as monotherapy in the treatment of serious gram negative infection

Empiric Carbapenem-Sparing Regimens and ESBL Infection

• 335 retrospective patient cohort: 249 received carbapenems and 86 received other active drugs (OADs)
• Most frequent OADs were aminoglycosides (N=43) and fluoroquinolones (N=20)
• Use of AODs was not associated with increased mortality, 14 day clinical failure, or length of hospital stay
  (Clin Infect Dis 2017; 65: 1615-23)
Aminoglycoside Toxicity
• Dose, time related: toxicity with less than 5 days of therapy has not been consistently demonstrated
• 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™)
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 $\leq 0.5 \mu\text{g/ml}$ for *S. aureus*, $\leq 0.25 \mu\text{g/ml}$ for enterococci, and $\leq 2 \mu\text{g/ml}$ 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.”
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)

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2016 IDSA HAP/VAP Guidelines

“We suggest prescribing 2 antipseudomonal antibiotics from different classes…only in patients with …risk factor for resistance.”

- Prior IV antibiotics
- Septic shock
- ARDS preceding VAP
- Five or more days hospitalization
- CRRT
Empirical Treatment of Ceftriaxone/Quinolone-Resistant Gram Negative Infection

- In order of preference from “clinically stable” (Top) to septic shock (Bottom):
  - Cefepime or carbapenem (*imipenem or meropenem, but not ertapenem*) 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. Ceftolozane-tazobactam
2. Ceftaroline
3. Colistin
4. Doripenem
5. Minocycline
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>Organism</td>
<td>Ceftobiprole or Ceftaroline MIC\textsubscript{90}</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 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)
**Colistin: Background**

- Structurally and pharmacologically similar to polymixin B
- Bactericidal activity derived from action as cationic detergent
- Active against MDR Pseudomonas and Acinetobacter
- Renal route of elimination
- Nephrotoxic and neurotoxic

### 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)

Effectiveness and safety of high-dose colistin

- Evaluation of 529 patients treated with either high-dose (9 million IU/daily) or lower-dose (3-6 million IU/daily)
- Mortality:
  - High dose: 50/144 (34.7%)
  - Lower dose: 165/385 (42.9%)
- Nephrotoxicity (RIFLE injury or higher):
  - OR, 2.12 [95% CI, 1.29-3.48] with high dose
  (Clin Infect Dis 2016; 63: 1605)
Intravenous Minocycline and Acinetobacter

- Primarily bacteriostatic, but bactericidal in combination with carbapenems or colistin
- Published experience to date is treatment of MDR Acinetobacter pneumonia (79% clinical and microbiological efficacy)
- More limited experience in the treatment of SSTI and bacteremia

(Drugs 2016; 76: 1467-76)

“2nd Generation” Cephalosporin-B-lactamase inhibitors: Ceftolozane/tazobactam (Zerbaxa®) and Ceftazidime/avibactam (Avycaz®)

- Approved for complicated UTIs and intra-abdominal infection
- Unlike piperacillin-tazobactam, must add metronidazole for intra-abdominal infection

(Clin Infect Dis 2016; 63: 234)
Ceftolozane/tazobactam (*Zerbaxa®*) and Ceftazidime/avibactam (*Avycaz®*)

- Both agents highly active against ESBL-producing *E. coli*
- Ceftazidime/avibactam more reliable than ceftolozane/tazobactam versus ESBL-producing *Klebsiella*
- Both agents, particularly ceftolozane/tazobactam, moderately likely to be active against MDR *Pseudomonas*
- Unpredictable vs *Acinetobacter*  
  (Clin Infect Dis 2016; 63: 234)

### 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>

*J Antimicrob Chemother 2014 Oct;69(10):2713-22*
Ceftazidime-avibactam and carbapenem-resistant Enterobacteriaceae infection

- 37 patients treated ≥3 days
- Clinical success: 22/37 (59%)
- Survival: 28/37 (76%)
- Recurrence: 5/22 (23%) clinical successes
- Microbiologic failure: 10/37 (27%)
  - Ceftazidime-avibactam resistance detected in 3/10 microbiologic failures
  (Clin Infect Dis 2016; 63: 1615)

Meropenem-vaborbactam (Vabomere®)

- First carbapenem-beta lactamase inhibitor combination
- Active against *Klebsiella pneumoniae* carbapenemase (KPC)-producing carbapenem-resistant Enterobacteriaceae (CRE)
- Approved for cUTI
TANGO II: Clinical cure with meropenem-vaborbactam vs BAT in treatment of CRE

<table>
<thead>
<tr>
<th>Time period</th>
<th>Meropenem-vaborbactam (N=28)</th>
<th>Best available therapy (BAT) (N=15)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of therapy</td>
<td>18/28 (64.3%)</td>
<td>6/15 (40%)</td>
<td>(-6.2% to 54.8%)</td>
</tr>
<tr>
<td>TOC</td>
<td>16/28 (57.1%)</td>
<td>4/15 (26.7%)</td>
<td>(1.6% to 59.4%)</td>
</tr>
</tbody>
</table>

ICAAC 2017

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.”
Timing of Treatment and Sepsis Mortality

- NY State required protocols for early identification and treatment of sepsis
- Of 49,331 patients, 40,696 (82.5%) had blood cultures, broad-spectrum antibiotic agents, lactate measurement, completed within 3 hours.
- More rapid administration of antibiotics, but not rapid initial fluid bolus were associate with lower risk of mortality
  
  (N Engl J Med 2017; 376: 2235-43)

Take Home Points

- Hospitalized patients, particularly those exposed to 3rd Generation cephalosporins and fluoroquinolones are at risk for superinfection (Pseudomonas, ESBL)
- Less sick patients with presumed Pseudomonas and ESBL can be empirically treated with cefepime or piperacillin-tazobactam therapy
Take Home Points

• If piperacillin-tazobactam is used, concomitant vancomycin should be avoided
• Meropenem (or imipenem) with tobramycin is likely the best empirical choice for septic patients
• Ertapenem and tigecycline have no role

Take Home Points

• Newer agents are available with potential value versus MDR isolates
  – Ceftolozane-tazobactam: Pseudomonas
  – Ceftazidime-avibactam: ESBL Klebsiella
  – Meropenem-vaborbactam: CRE
• Rapid administration of antibiotics, but not IV fluids, is associated with decreased mortality
• De-escalation of antibacterials reduces risk for superinfection and resistance