GORILLACILLINS IN THE ICU: From SPACE and Beyond...

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Overview

- Gorillacillins
  1. How do we use them?
     - Principles of Gorillacillin Use
  2. What are they?
     - The Gorillacillins
  3. When do we use them?
     - Gorillacillins vs. AmpC (SPACE) & ESBL
  4. What’s up & coming?
     - Future Gorillacillins in the Pipeline

Carbapenem

- Doripenem
  - MOA: Binds to PBP; inhibits cell wall synthesis
  - PK/PD: Fluids & tissues (bile, gallbladder, peritoneal fluid, urine)
    Non-CYP metabolism/renal excretion
  - Dose: 500 mg IV q8h
    - Renal impairment
      - CrCl 30-50 mL/min: 250 mg IV q8h
      - CrCl 11-29 mL/min: 250 mg IV q12h
    - HD: ~52% dialyzed; continuous hemodiafiltration: 250 mg q12h
  - ADR:
    - >10%: h/a (4-16%), N&V (4-12%), diarrhea (6-11%)
    - 1-10%: Rash, phlebitis, anemia, transaminitis
  - Drug Interactions:
    - Probenecid: ↑ doripenem AUC by 75%
    - Valproic acid: ↓ valproate

Conflicts of Interest

- None to declare
Carbapenem

**Indications:**
- Nosocomial pneumonia, including VAP
  - HAP & VAP (P R MC OL)
  - Doripenem vs. piperacillin-tazobactam (N=448)
    - Cure rate: 81.3 vs. 79.8% (non-inferior)
    - All-cause mortality (28d): 13.8 vs. 14.8%
- VAP (P R MC OL)
  - (Chastre et al. Crit Care Med 2008;36:1089-96.)
- Doripenem vs. imipenem-cilastatin (N=531)
  - Cure rate: 68.3 vs. 64.2%
  - All-cause mortality (28d): 10.8 vs. 9.5%

**Place in ICU Practice:**
- Nosocomial pneumonia (HAP & VAP)
- Complicated intraabdominal infections
- Complicated UTI/Pyelonephritis
- Efficacy against carbapenem-resistant *Pseudomonas*
- Impact on ICU flora
- Acinetobacter
- AmpC (SPACE)/ESBL
- Meningitis

**Ongoing Studies:**
- VAP, usage patterns

**Carbapenem**

**Indications:**
- Complicated intraabdominal infection
  - Doripenem vs. meropenem (P R DB MC N-I) (N=476)
    - Clinical cure: 77.9 vs. 78.9%
    - Clinical cure in micro evaluable: 85.9 vs. 85.3%
- Complicated UTI, including pyelonephritis
  - Doripenem vs. levofloxacin (P R DB MC) (N=748)
    - Micro cure: 82.1 vs. 83.4%
    - Clinical cure: 95.1 vs. 90.2%

**Class:**
- 5th generation

**MOA:**
- Binds to PBP (PBP2a, 2x, 3); inhibits cell wall synthesis

**PK/PD:**
- Soft tissue (lung, liver, kidney, skin)
- Activated by esterases; renal excretion

**Dose:**
- 500 mg IV q8-12h (q12h for Gram +; q8h for Gram –)
  - Renal impairment
    - CrCl 30-<50 mL/min: 500 mg IV q12h
    - CrCl 10-29 mL/min: 250 mg IV q12h
    - CrCl <10 mL/min or HD: Not studied

**ADR:**
- 1-10%: h/a (5%), nausea (9%), taste disturbance (6%), diarrhea (5%), phlebitis (2%), ↑ ALT (2%)

**Drug Interactions:**
- None

**Carbapenem**

**Indications:**
- Complicated UTI, including pyelonephritis
  - Gram +
  - Gram –

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- None

**Carbapenem**

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**Carbapenem**

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**Ongoing Studies:**
- VAP, usage patterns

**Cephalosporin**

**Ceftobiprole medocaril**

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    - CrCl 30-<50 mL/min: 500 mg IV q12h
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    - CrCl <10 mL/min or HD: Not studied

**ADR:**
- 1-10%: h/a (5%), nausea (9%), taste disturbance (6%), diarrhea (5%), phlebitis (2%), ↑ ALT (2%)

**Drug Interactions:**
- None
**Ceftobiprole medocaril**

- **Spectrum:**
  - **ANTIBIOTIC**
  - **GRAM +**
  - **GRAM -**
  - **ANAEROBES**
  - **Ceftobiprole**
    - Staph, MRSA, Strep, E. faecalis, VRE faecalis
    - Enterobacteriaceae*, H. flu, Moraxella, Pseudomonas
    - Peptostreptococcus, Propionibacterium, Clostridium sp.
  - **Ceftazidime**
    - Strep
    - Enterobacteriaceae*, H. flu, Moraxella, Pseudomonas
    - Peptostreptococcus
  - **Cefotaxime/Ceftazidime**
    - Staph, Strep
    - Enterobacteriaceae*, H. flu, Moraxella
    - Peptostreptococcus
  - **Cefepime**
    - Staph, Strep
    - Enterobacteriaceae*, H. flu, Moraxella, Pseudomonas
    - Peptostreptococcus

*Enterobacteriaceae = Citrobacter, Enterobacter, E.coli, Klebsiella, Proteus, Salmonella, Serratia

- **NOT effective against**
  - E. faecium, Acinetobacter, ESBL

**Indications:**
- **Complicated skin and skin structure infections**
- **Gram+ complicated skin infections** (R DB MC NI, N=784)
  - Ceftobiprole 500 mg IV q12h vs. vancomycin
  - Clinical cure: 93.3 vs. 93.5%
  - MRSA cure: 91.8 vs 90%
- **Diabetic foot infection** (R DB MC NI, N=828)
  - Ceftobiprole 500 mg IV q8h vs. vancomycin/cefazidime
  - Clinical cure: 90.5 vs. 90.2%
  - MRSA cure: 89.7 vs. 86.1%
- **Pseudomonas cure:**
  - 86.7 vs. 100%

**Place in ICU Practice:**
- **Complicated skin and skin structure infections**
  - Polymicrobial with MRSA
- **Nosocomial pneumonia (HAP & VAP)**
  - Ceftobiprole vs. linezolid/cefazidime (R DB MC NI, N=781)
    - Clinical cure: 69.3 vs. 71.6%
    - VAP clinical cure: 38.5 vs. 56.7% (p<0.05)
- **Ongoing Studies:**
  - CAP, PK-OM, PK-ICU

**Bottom-line:**
- Ceftobiprole good MRSA & polymicrobial (Pseudomonas) activity
  - Limit to infections with MRSA & polymicrobial
- Further studies in intraabdominal infections, VAP, osteomyelitis, & febrile neutropenia required
- Place in practice determined by further studies

**PK/PD:**
- Extensive tissue distribution, pleural fluid
- Hepatic metabolism
  - T>MIC with AUC 2-4x MIC
- **Dose:**
  - 100 mg IV, then 50 mg IV q12h
  - Hepatic impairment
    - Child-Pugh Class A/B: No adjustment
    - Child-Pugh Class C: 100 mg IV, then 25 mg IV q12h
    - HD: No change
- **ADR:**
  - >10%: N/V (18-21%), diarrhea (12%)
  - 2-10%: H/a (6%), anemia (4%), ↑ LFT (4%)
- **Drug Interactions:**
  - Warfarin: ↑ INR (monitor)
Glycylcycline

- **Tigecycline**
  - **Spectrum:**
    | GRAM + | GRAM - | ANAEROBES | ATYPICALS |
    |----------------|-----------|------------|------------|
  - **NOT effective against**
    - Pseudomonas, Proteus, Morganella

- **Indications:**
  - **Complicated Skin and Skin Structure Infection**
    - Tigecycline vs. vancomycin/aztreonam (R DB) (N=1116)
    - Cure rate: 79.7 vs. 81.9%
  - **Complicated Intraabdominal Infection**
    - Tigecycline vs. imipenem-cilastatin (R DB) (N=1642)
    - Microbiological cure rate: 80.2 vs. 81.5%
  - **Community-acquired Pneumonia**
    - Tigecycline vs. levofloxacin (N=846)
    - Clinical cure: 89.7 vs. 86.3%
  - **Nosocomial Pneumonia (HAP & VAP)**
    - Tigecycline vs. imipenem-cilastatin (R DB)
    - Tigecycline inferior in 2 primary endpoints & in VAP subgroup analysis
    - Ongoing study using 2 doses of tigecycline

- **Place in ICU Practice:**
  - Complicated intraabdominal infections
    - MRSA/VRE & polymicrobial
  - Complicated skin and skin structure infection
    - MRSA/VRE & polymicrobial
  - MRSA, VRE, ESBL, Acinetobacter, C. difficile
  - HAP/VAP
  - Catheter infections, PK-bone, Mycobacterium, HAP, diabetic foot osteomyelitis, VRE/MRSA, carbapenem-resistant Gram-negative

- **Bottom-line:**
  - Tigecycline reserved for infections with MRSA/VRE & polymicrobial
  - Intraabdominal infection
  - Alternative for MDR
    - ESBL, Acinetobacter
  - Spectrum too broad for CAP
    - ? HAP/VAP
  - Does NOT cover Pseudomonas
  - ? Clinical failure with bacteremia

Gorillacillins vs. AmpC & ESBL

- **AmpC (SPACE)**
  - Hydrolyze penicillins, 1st, 2nd, & 3rd gen cephalosporin/cephamycins; resist β-lactamase inhibitors (clavulanate, tazobactam)

  - **Treatment:**
    - 1st line: Carbapenem
    - 2nd line: FQ, TMP-SMX
    - Aminoglycoside
    - 3rd line: Cefepime - Stable against AmpC Enterobacteriaceae
    - Colistimethate - Based on in vitro activity
    - Tigecycline - May be option in absence of bacteremia
  - **Do not use:** β-lactamase inhibitor combination
    - 2nd, 3rd cephalosporin
Gorillacillins vs. AmpC & ESBL

**ESBL**
- Hydrolyze penicillin, 3<sup>rd</sup> gen cephalosporin, aztreonam, β-lactamase inhibitor combos; often resistant to AMG, FQ, TMP-SMX

**General Principles:**
1. Avoid cephalosporins (1<sup>st</sup> to 4<sup>th</sup> gen)
   - “Inoculum effect” causes bugs to look susceptible in lab, BUT if numbers high in vivo MIC increases to point that organism becomes resistant
3. Small studies carbapenem as 1<sup>st</sup> line significantly lower mortality (Paterson DL et al. Clin Infect Dis 2004;39:31-7.)
   - ESBL Klebsiella bacteremia mortality 4.8 vs. 27.6% (FQ)
   - ESBL pneumonia positive response in 10/10 patients receiving carbapenem vs. 9/13 receiving cefepime
   - Do not use 2<sup>nd</sup>, 3<sup>rd</sup> cephalosporin

**In Clinical Practice (ATS/IDSA HAP/VAP)**

**Future Gorillacillins in the Pipeline**

<table>
<thead>
<tr>
<th>GRAM +</th>
<th>GRAM + &amp; GRAM -</th>
<th>GRAM +, GRAM - &amp; ANAEROBES</th>
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<tbody>
<tr>
<td>Dalbavancin (lipoglycopeptide)</td>
<td>Ceftriaxone (cephalosporin)</td>
<td>Tomopenem (carbapenem)</td>
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<tr>
<td>Oritavancin (glycopeptide)</td>
<td>Iclaprim (diaminopyrimidine)</td>
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<td>Telavancin (glycopeptide)</td>
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<td>Radezolid (oxazolidinone)</td>
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**Questions?**

Courtesy of Euan Mactavish
(http://supergorillas.blogspot.com/)