GORILLACILLINS IN THE ICU:
From SPACE and Beyond…

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Conflicts of Interest

- None to declare

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

Principles of Gorillacillin Use

1. Treat broadly
2. Don't delay
3. Know the organism
4. Know your environment
5. Remove the source
6. Narrow down when possible
7. Don't over treat
8. Have a threshold for giving antibiotics
9. Have criteria for stopping
10. Talk with the experts

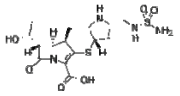
(Kollef. Crit Care 2001;5:189-95, Cunha. Crit Care Clin 2008;24:313-34, Kumar. Crit Care Clin 2009;25:733-51, Lawrence et al. Am J Respir Crit Care Med 2009;179:434-8.)

The Gorillacillins

- **The New**
  - Carbapenem
    - ***Doripenem***
    - Ertapenem
    - Imipenem-cilastatin
    - Meropenem
  - Cephalosporin
    - Cefepime
    - ***Ceftobiprole***
  - Glycylcycline
    - ***Tigecycline***
  - Lipopeptide
    - Daptomycin
- **The Old**
  - Penicillin
    - Piperacillin-tazobactam
    - Ticarcillin-clavulanate
  - Polymyxin
    - Colistin
  - Other
    - Chloramphenicol

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

Carbapenem

- **Doripenem**
  - Spectrum:

CARBAPENEM	GRAM +	GRAM -	ANAEROBES
Doripenem	*Staph*, *Strep*, *E. faecalis*	Enterobactericiae (AmpC & ESBL), *H. flu*, *Moraxella*, ***Pseudomonas***, ***Acinetobacter***	*Bacteroides*, Peptostreptococus, *Prevotella*, *Clostridium*, *Fusobacterium*
Ertapenem	*Staph*, *Strep*	Enterobactericiae (AmpC & ESBL), *H. flu*, *Moraxella*	*Bacteroides*, Peptostreptococus, *Prevotella*, *Clostridium*, *Fusobacterium*
Imipenem-cilastatin	*Staph*, *Strep*, *E. faecalis*	Enterobactericiae (AmpC & ESBL), *H. flu*, *Moraxella*, *Pseudomonas*, *Acinetobacter*	*Bacteroides*, Peptostreptococus, *Prevotella*, *Clostridium*, *Fusobacterium*
Meropenem	*Staph*, *Strep*, *E. faecalis*	Enterobactericiae (AmpC & ESBL), *H. flu*, *Moraxella*, *Pseudomonas*, *Acinetobacter*, ***Burkholderia***	*Bacteroides*, Peptostreptococus, *Prevotella*, *Clostridium*, *Fusobacterium*

  - **NOT effective against**
    - *E. faecium*, *Burkholderia cepacia*, *Stenotrophomonas*

Carbapenem

- **Doripenem**
  - Indications:
    - **Nosocomial pneumonia, including VAP**
      - HAP & VAP (P R MC OL)
        (Réa-Neto et al. Curr Med Res Opin 2008;24:2113-26.)
      - Doripenem vs. piperacillin-tazobactam (N=448)
        - Cure rate: 81.3 vs. 79.8% (non-inferior)
        - All-cause mortality (28d): 13.8 vs. 14.6%
      - 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%

Carbapenem

- **Doripenem**
  - Indications:
    - **Complicated intraabdominal infection**
      - Doripenem vs. meropenem (P R DB MC N-I) (N=476)
        (Lucasti et al. Clin Ther 2008;30:868-83.)
        - 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)
        (Naber et al. Antimicrob Agents Chemother. 2009;53:3782-92.)
        - Micro cure: 82.1 vs. 83.4%
        - Clinical cure: 95.1 vs. 90.2%

Carbapenem

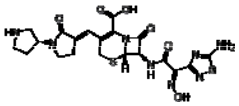
- **Doripenem**
  - Place in ICU Practice:
    - Nosocomial pneumonia (HAP & VAP)
    - Complicated intraabdominal infections
    - Complicated UTI/pyelonephritis
    - ? Efficacy against carbapenem-resistant *Pseudomonas*
    - ? Impact on ICU flora
    - ? *Acinetobacter*
    - ? AmpC (SPACE)/ESBL
    - ? Meningitis
  - Ongoing Studies:
    - VAP, usage patterns

Carbapenem

- **Doripenem**
  - Bottom-line:
    - Similar to other carbapenems
      - Imipenem-cilastatin & meropenem
    - Significance of lower MICs for Gram-negatives remains to be determined
      - Clinically?
      - Microbiologically?

Cephalosporin

- **Ceftobiprole medocaril**



  - 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

Cephalosporin

- **Ceftobiprole medocaril**
  - Spectrum:

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

*Enterobactericiae – *Citrobacter, Enterobacter, E.coli, Klebsiella, Proteus, Salmonella, Serratia*

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

Cephalosporin

- **Ceftobiprole medocaril**
  - Indications:
    - **Complicated skin and skin structure infections**
      - **Gram+ complicated skin infections** (R DB MC NI, N=784)
        (Noel et al. Antimicrob Agents Chemother 2008;52:37-44.)
        - 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)
        (Noel et al. Clin Infect Dis 2008;46:647-55.)
        - Ceftobiprole 500 mg IV q8h vs. vancomycin/ceftazidime
        - Clinical cure: 90.5 vs. 90.2%
        - MRSA cure: 89.7 vs. 86.1%
        - Pseudomonas cure: 86.7 vs. 100%

Cephalosporin

- **Ceftobiprole medocaril**
  - Indications:
    - **CAP**
      (Nicholson et al. ATS International Conference 2008 [Abstract])
      - Ceftobiprole vs. ceftriaxone±linezolid (R DB) (N=666)
        - Cure cure: 86.7 to 87.6%
    - **? Nosocomial pneumonia (HAP & VAP)**
      (Noel et al. ICAAC & IDSA Meeting 2008 [Abstract])
      - Ceftobiprole vs. linezolid/ceftazidime (R DB MC) (N=781)
        - Clinical cure: 69.3 vs. 71.6%
        - VAP clinical cure: 38.5 vs. 56.7% (p<0.05)

Cephalosporin

- **Ceftobiprole medocaril**
  - Place in ICU Practice:
    - Complicated skin and skin structure infections
      - Polymicrobial with MRSA
    - ? Nosocomial pneumonia (HAP) not VAP
    - ? Intraabdominal infection
    - ? Febrile neutropenia
    - ? Diabetic foot infection/osteomyelitis
      - Polymicrobial with MRSA
    - ?AmpC (SPACE)
  - Ongoing Studies:
    - CAP, PK-OM, PK-ICU

Cephalosporin

- **Ceftobiprole medocaril**
  - 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

Glycylcycline

- **Tigecycline**
  - MOA: Binds to 30S ribosomal subunit; inhibits protein synthesis
  - 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 (18-26%), diarrhea (12%)
    2-10%: h/a (6%), anemia (4%), ↑ LFT (4%)
  - Drug Interactions:
    Warfarin: ↑ INR (monitor)

Glycylcycline

- **Tigecycline**
  - Spectrum:

GRAM +	GRAM -	ANAEROBES	ATYPICALS
S. aureus, **MRSA**, **S. epi**, S. pneumoniae, **E. faecalis/ faecium, VRE**	*Enterobactericiae, **ESBL**, **? Acinetobacter**, H. flu, Moraxella, ? Stenotrophomonas*	*Bacteroides fragilis, Clostridium perfringens, ? **C. difficile**, Peptostreptococcus, Propionibacterium*	*C. pneumoniae, Mycoplasma*

  - **NOT effective against**
    - *Pseudomonas, Proteus, Morganella*

Glycylcycline

- **Tigecycline**
  - Indications:
    - **Complicated Skin and Skin Structure Infection**
      (Ellis-Grosse et al. CID 2005;41:S341-53)
      - Tigecycline vs. vancomycin/aztreonam (R DB) (N=1116)
        - Cure rate: 79.7 vs. 81.9%
    - **Complicated Intraabdominal Infection**
      (Babinchak et al. CID 2005;41:S354-67.)
      - Tigecycline vs. imipenem-cilastatin (R DB) (N=1642)
        - Microbiological cure rate: 80.2 vs. 81.5%

Glycylcycline

- **Tigecycline**
  - Indications:
    - **Community-acquired Pneumonia**
      (Tanaseanu et al. Diagn Microbiol Infect Dis 2008;61:329-38.)
      - Tigecycline vs. levofloxacin (N=846)
        - Clinical cure: 89.7 vs. 86.3%
    - **Nosocomial Pneumonia (HAP & VAP)**
      (Unpublished)
      - Tigecycline vs. imipenem-cilastatin (R DB)
        - Tigecycline inferior in 2 primary endpoints & in VAP subgroup analysis
        - Ongoing study using 2 doses of tigecycline

Glycylcycline

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

Glycylcycline

- **Tigecycline**
  - 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-lactamse inhibitors (clavulanate, tazobactam)*
  - Treatment:
    - 1st line: Carbapenem
    - 2nd line: FQ
      TMP-SMX
      Aminoglycoside
    - 3rd line: Cefepime - Stable against AmpC Enterobactericiae
      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, 3rd gen cephalosporin, aztreonam, β-lactamase inhibitor combos; often resistant to AMG, FQ, TMP-SMX*

General Principles:

1. Avoid cephalosporins (1st to 4th gen)
2. Stay away from β-lactamase inhibitor combos to avoid "inoculum effect" & development of porin deficient mutants
   (Martinez-Martinez L et al. Antimicrob Agents Chemother 1996;40:342-8.)
   - "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 1st 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 carbepenem vs. 9/13 receiving cefepime

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Gorillacillins vs. AmpC & ESBL

- **ESBL**
  - Treatment:
    - 1st line: Carbapenem –
      Carbapenem superior to FQ or β-lactams in small studies
    - 2nd line: FQ
      TMP-SMX
      Aminoglycoside
    - 3rd-line: β-lactamase inhibitor combos –
      Limited experience in serious infections
      Colistimethate –
      Based on *in vitro* activity
      Tigecycline –
      May be option in absence of bacteremia
    - **Do not use** 2nd, 3rd cephalosporin

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Gorillacillins vs. AmpC & ESBL

- In Clinical Practice (ATS/IDSA HAP/VAP)
  (Am J Respir Crit Care Med 2005; 171:388–416.)

TABLE 4. INITIAL EMPIRIC THERAPY FOR HOSPITAL-ACQUIRED PNEUMONIA, VENTILATOR-ASSOCIATED PNEUMONIA, AND HEALTHCARE-ASSOCIATED PNEUMONIA IN PATIENTS WITH LATE-ONSET DISEASE OR RISK FACTORS FOR MULTIDRUG-RESISTANT PATHOGENS AND ALL DISEASE SEVERITY

Potential Pathogens	Combination Antibiotic Therapy*
Pathogens listed in Table 3 and MDR pathogens *Pseudomonas aeruginosa* *Klebsiella pneumoniae* (ESBL+)† *Acinetobacter* species‡	Antipseudomonal cephalosporin (cefepime, ceftazidime) or Antipseudomonal carbepenem (imipenem or meropenem) or β-Lactam/β-lactamase inhibitor (piperacillin–tazobactam) plus Antipseudomonal fluoroquinolone‖ (ciprofloxacin or levofloxacin) or Aminoglycoside (amikacin, gentamicin, or tobramycin) plus
Methicillin-resistant *Staphylococcus aureus* (MRSA) *Legionella pneumophila*§	Linezolid or vancomycin§

* *See* Table 5 for adequate initial dosing of antibiotics. Initial antibiotic therapy should be adjusted or streamlined on the basis of microbiologic data and clinical response to therapy.
† If an ESBL+ strain, such as *K. pneumoniae*, or an *Acinetobacter* species is suspected, a carbapenem is a reliable choice. If *L. pneumophila* is suspected, the combination antibiotic regimen should include a macrolide (e.g., azithromycin) or a fluoroquinolone (e.g., ciprofloxacin or levofloxacin) should be used rather than an aminoglycoside.
‡ If MRSA risk factors are present or there is a high incidence locally.

TABLE 5. INITIAL INTRAVENOUS, ADULT DOSES OF ANTIBIOTICS FOR EMPIRIC THERAPY OF HOSPITAL-ACQUIRED PNEUMONIA, INCLUDING VENTILATOR-ASSOCIATED PNEUMONIA, AND HEALTHCARE-ASSOCIATED PNEUMONIA IN PATIENTS WITH LATE-ONSET DISEASE OR RISK FACTORS FOR MULTIDRUG-RESISTANT PATHOGENS

Antibiotic	Dosage*
Antipseudomonal cephalosporin	
Cefepime	1–2 g every 8–12 h
Ceftazidime	2 g every 8 h
Carbepenems	
Imipenem	500 mg every 6 h or 1 g every 8 h
Meropenem	1 g every 8 h
β-Lactam/β-lactamase inhibitor	
Piperacillin–tazobactam	4.5 g every 6 h
Aminoglycosides	
Gentamicin	7 mg/kg per d†
Tobramycin	7 mg/kg per d†
Amikacin	20 mg/kg per d†
Antipseudomonal quinolones	
Levofloxacin	750 mg every d
Ciprofloxacin	400 mg every 8 h
Vancomycin	15 mg/kg every 12 h‡
Linezolid	600 mg every 12 h

* Dosages are based on normal renal and hepatic function.
† Trough levels for gentamicin and tobramycin should be less than 1 μg/ml, and for amikacin they should be less than 4–5 μg/ml.
‡ Trough levels for vancomycin should be 15–20 μg/ml.

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Future Gorillacillins in the Pipeline

GRAM +	GRAM + & GRAM -	GRAM +, GRAM -, & ANAEROBES
Dalbavancin (lipoglycopeptide)	**Ceftaroline** (cephalosporin)	**Tomopenem** (carbapenem)
Oritavancin (glycopeptide)	**Iclaprim** (diaminopyrimidine)	
Telavancin (glycopeptide)		
Radezolid (oxazolidinone)		

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Questions?

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

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