



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

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Conflicts of Interest

- None to declare



Overview

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



Principles of Gorillacillin Use

- Treat broadly
- Don't delay
- Know the organism
- Know your environment
- Remove the source
- Narrow down when possible
- Don't over treat
- Have a threshold for giving antibiotics
- Have criteria for stopping
- 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.)



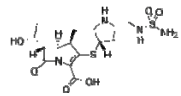
The Gorillacillins

- | | |
|---|---|
| <ul style="list-style-type: none"> The New <ul style="list-style-type: none"> Carbapenem <ul style="list-style-type: none"> Doripenem Ertapenem Imipenem-cilastatin Meropenem Cephalosporin <ul style="list-style-type: none"> Cefepime Ceftobiprole Glycylcycline <ul style="list-style-type: none"> Tigecycline Lipopeptide <ul style="list-style-type: none"> Daptomycin | <ul style="list-style-type: none"> The Old <ul style="list-style-type: none"> Penicillin <ul style="list-style-type: none"> Piperacillin-tazobactam Ticarcillin-clavulanate Polymyxin <ul style="list-style-type: none"> Colistin Other <ul style="list-style-type: none"> 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	<i>Staph, Strep, E. faecalis</i>	Enterobacteriaceae (AmpC & ESBL), <i>H. flu, Moraxella, Pseudomonas, Acinetobacter</i>	<i>Bacteroides, Peptostreptococcus, Prevotella, Clostridium, Fusobacterium</i>
Ertapenem	<i>Staph, Strep</i>	Enterobacteriaceae (AmpC & ESBL), <i>H. flu, Moraxella</i>	<i>Bacteroides, Peptostreptococcus, Prevotella, Clostridium, Fusobacterium</i>
Imipenem-cilastatin	<i>Staph, Strep, E. faecalis</i>	Enterobacteriaceae (AmpC & ESBL), <i>H. flu, Moraxella, Pseudomonas, Acinetobacter</i>	<i>Bacteroides, Peptostreptococcus, Prevotella, Clostridium, Fusobacterium</i>
Meropenem	<i>Staph, Strep, E. faecalis</i>	Enterobacteriaceae (AmpC & ESBL), <i>H. flu, Moraxella, Pseudomonas, Acinetobacter, Burkholderia</i>	<i>Bacteroides, Peptostreptococcus, Prevotella, Clostridium, Fusobacterium</i>

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

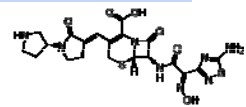
Doripenem

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, <i>E. faecalis</i> , VRE <i>faecalis</i>	Enterobacteriaceae*, <i>H. flu</i> , <i>Moraxella</i> , <i>Pseudomonas</i>	<i>Peptostreptococcus</i> , <i>Propionibacterium</i> , <i>Clostridium sp.</i>
Ceftazidime	Strep	Enterobacteriaceae*, <i>H. flu</i> , <i>Moraxella</i> , <i>Pseudomonas</i>	<i>Peptostreptococcus</i>
Cefotaxime/Ceftriaxone	Staph, Strep	Enterobacteriaceae*, <i>H. flu</i> , <i>Moraxella</i>	<i>Peptostreptococcus</i>
Cefepime	Staph, Strep	Enterobacteriaceae*, <i>H. flu</i> , <i>Moraxella</i> , <i>Pseudomonas</i>	<i>Peptostreptococcus</i>

*Enterobacteriaceae – *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	Enterobacteriaceae, 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 intraabdominal 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 -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, 3rd gen cephalosporin, aztreonam, β -lactamase inhibitor combos; often resistant to AMG, FQ, TMP-SMX

General Principles:

- Avoid cephalosporins (1st to 4th gen)
- 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
- 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 carbapenem vs. 9/13 receiving cefepime

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

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 MDK pathogens	Antipseudomonal cephalosporin (cefepime, ceftazidime) or
<i>Pseudomonas aeruginosa</i>	Antipseudomonal carbapenem (meropenem or imipenem) or
<i>Klebsiella pneumoniae</i> (ESBL) [†]	β -lactam/ β -lactamase inhibitor (piperacillin-tazobactam) plus
<i>Acinetobacter</i> species [‡]	Antipseudomonal fluoroquinolone [§] (ciprofloxacin or levofloxacin) or
	Aminoglycoside (amikacin, gentamicin, or tobramycin) plus
Methicillin-resistant staphylococci (MRSA)	Linezolid or vancomycin [¶]
<i>Legionella pneumophila</i> [¶]	

* See Table 5 for adequate initial dosing of antibiotics. Initial antibiotic therapy should be adjusted or discontinued 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
Carbapenems	
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 μ g/ml, and for amikacin they should be less than 4–5 μ g/ml.
[‡] Trough levels for vancomycin should be 15–20 μ g/ml.

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)		

Questions?



Courtesy of Euan Mactavish
<http://supergorillas.blogspot.com/>