UNIVERSITY OF LIVERPOOL | ANTIMICROBIAL PHARMACODYNAMICS AND THERAPEUTICS

PK-PD Concepts to optimize the treatment of Pneumonia: a clinical perspective

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- "In an era of increasing resistance, we should select agents and doses that provide drug concentrations that exceed the magnitude of the **PK/PD index** required both **for efficacy and to combat the emergence and spread of bacterial resistance**" (Craig WA, 2001)

- IDSA/ATS 2005 guidelines adopted these concepts specifically for HAP

- In the treatment of pneumonia, is it enough to use PK/PD targets referred to antibiotic serum concentrations…or should we be guided by PK/PD indexes at the site of infection?

- Are these targets at the site of infection (i.e ELF PK/PD) correlated to clinical outcomes in patients?

Overview

1. PK-PD considerations at the site of infection (lung)
2. Epithelial lining fluid (ELF) studies in humans
3. PK-PD studies in pneumonia that are correlated with patient clinical outcomes
4. Future directions
5. Conclusions

PK/PD Considerations at the site of infection

- Free concentrations in plasma are often viewed as an acceptable approximation for free concentrations at the site of infection, but this is not always the case
- Opportunity exists to include additional compartments in PK model building phase and perform simulations for concentrations at site of infection, however…

PK sampling is required in each compartment

to properly estimate exposure profiles!

Lodise TP, Drusano GL. Crit Care Clin. 2011 Jan;27(1):1-18

PK/PD Considerations at the lung

1) Method for measuring antibiotic concentrations in the lungs

- Determination of drug concentration in **epithelial lining fluid (ELF)** is currently the most widely employed method to estimate antibiotic exposure for extracellular respiratory tract pathogens[1,2]
- **The 'apparent' volume of ELF must be estimated with Urea or other endogenous marker:**

$$AB_{ELF} = AB_{BAL} * (urea_{SER}/urea_{BAL})$$

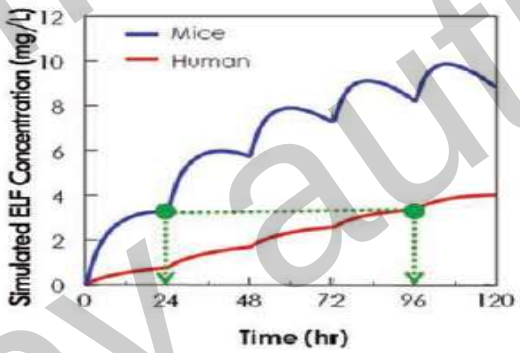
1. Rodvold KA, et al. Clin Pharmacokinet 2011; 50 (10): 637-664.
2. Drusano GL, et al. Antimicrob Agents Chemother, Feb. 2002, p. 586–589

PK/PD Considerations at the lung

2) Pharmacodynamic target

- The PK/PD targets in ELF derived from animal models of pneumonia and bridged to humans (PK in healthy volunteers)[1,2]
- Penetration in ELF/bloodstream should consider cumulative exposure over time

ORITAVANCIN[3]

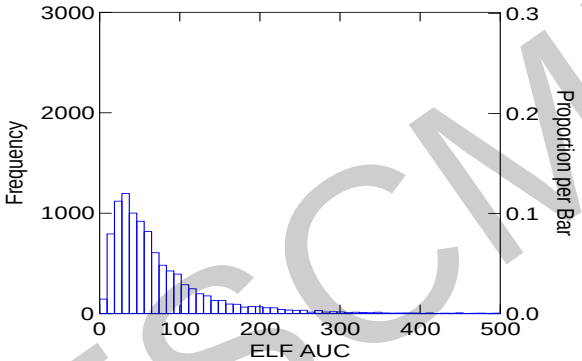


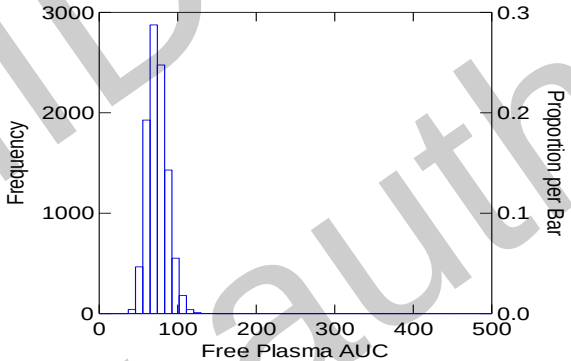
1. Drusano GL et al. Antimicrob Agents Chemother. 2011 Jul;55(7):3406-12.
2. Rodvold KA et al. Antimicrob Agents Chemother. 2009 Aug;53(8):3294-301.
3. Bhavnani SM et al. ICAAC.2008. Abstract A-51.

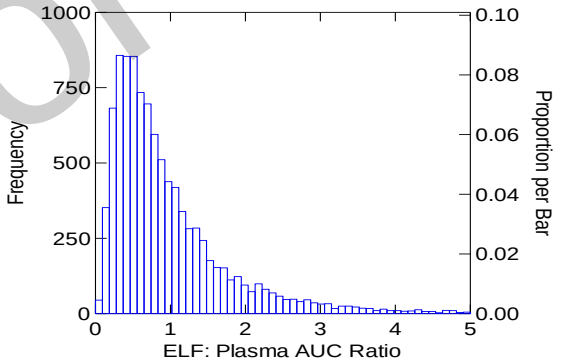
PK/PD Considerations at the lung

3) Inter-patient PK variability in bloodstream and site of infection

Cannot only rely on mean/ median PK point estimates

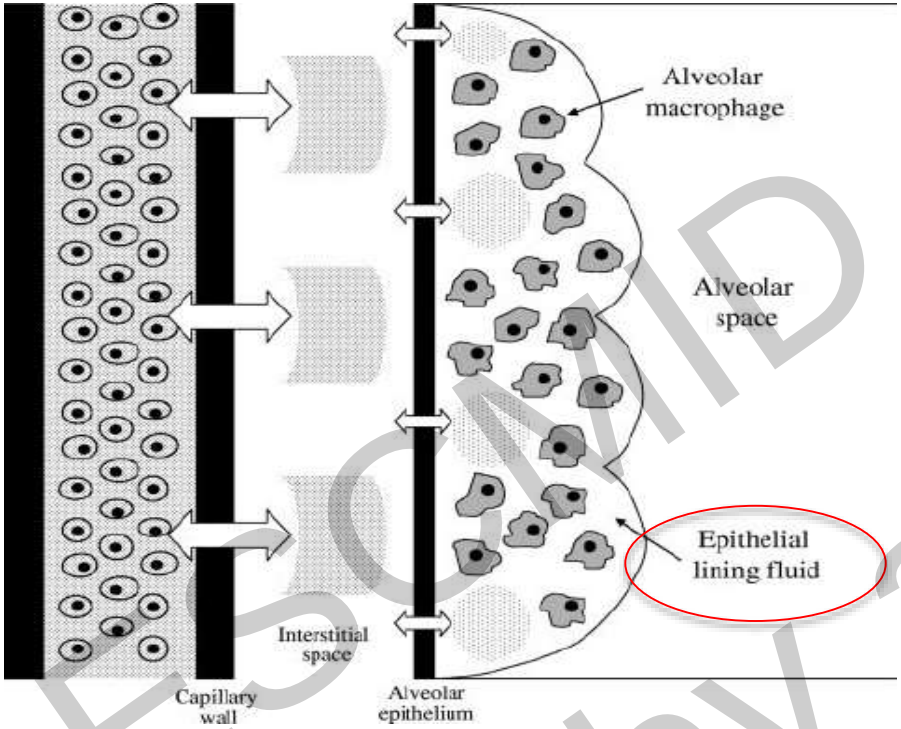






Lodise TP et al. Antimicrob Agents Chemother. 2008 Jul;52(7):2300-4

PK sampling required in each compartment : ELF concentrations of antibiotics



1) Anatomical/Penetration capacity:

- Protein binding
- Lipophilicity and diffusibility (MW)*

2) ELF measurement and cell effect:

- Cellular components: MA lysis
- "Apparent" volume of ELF sampled by BAL corrected for drug-free saline

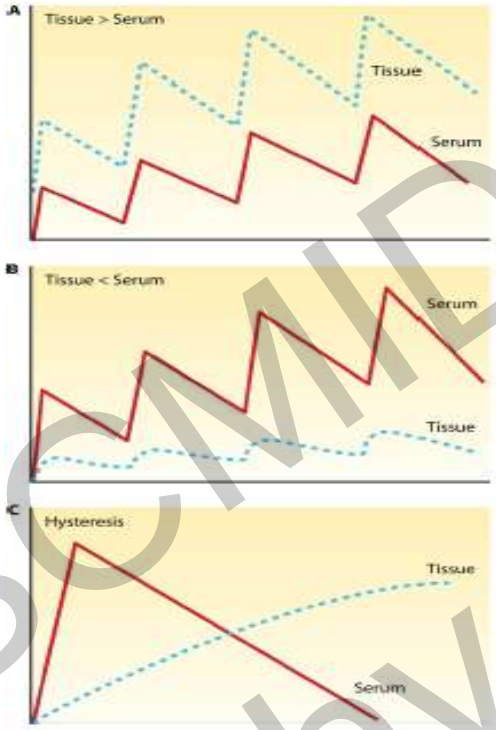
3) Technical errors:

- Dwelling time of fluid during BAL >1min, contamination of BAL with blood urea

Kiem and Shentag. AAC 2008. 52 (1): p.24-36

*MW= Molecular weight

ELF/bloodstream concentration ratios can be uninformative due to system hysteresis



ELF > Serum

- Macrolides
- Oxazolidinones
- Fluoroquinolones

Serum > ELF

- Betalactams
- Aminoglycosides
- Glycopeptides

Serum ≈ ELF, but hysteresis

- Meropenem

Felton TW et al. CMR. 2014. 27(1):68-88. Rodvold KA, et al. Clin Pharmacokinet 2011; 50 (10): 637-664.

ELF Studies in humans

- Aim: 1) to determine drug penetration into ELF
- Involve either healthy adult subjects or patients undergoing diagnostic bronchoscopy
- Discordant lung penetration amongst same class (i.e cephalosporins) independent of protein binding or structure: **ceftazidime** (20-30 %)[1,2], **cefepime** (100%)[3], **ceftobiprole** (≈ 4-55%, median 15%)[4]**-different ELF penetrations between mice SA pneumonia model and humans!**-, **cefditoren** (33 ±48%)[5]

1. Boselli E et al. Intensive Care Med. 2004. 30: 989-991. 2. Nicolau DP et al. JAC. 2015; 70: 2862-69 3. Boselli E et al. Crit Care Med. 2003; 31(8):2102-06. 4. Rodvold KA et al. AAC. 2009;53(8): 3294-3301. 5. Lodise TP et al. AAC.2008; 52 (6): 1945-51

A Phase 3 Randomized Double-Blind Comparison of Ceftobiprole Medocaril Versus Ceftazidime Plus Linezolid for the Treatment of Hospital-Acquired Pneumonia

Clinical Infectious Diseases 2014;59(1):51–61

The importance of ELF studies before phase 2 and 3 studies!!

Table 2. Primary Endpoint: Clinical Cure at Test of Cure (Intent-to-Treat and Clinically Evaluable Analysis Sets)

	Ceftobiprole		Ceftazidime/Linezolid			
Analysis Set Group	No.	No.[a] (%)	No.	No.[a] (%)	Difference (%)[b]	(95% CI)[c]
Intent-to-treat						
All patients	391	195 (49.9)	390	206 (52.8)	−2.9	(−10.0 to 4.1)
HAP (excluding VAP)	287	171 (59.6)	284	167 (58.8)	0.8	(−7.3 to 8.8)
VAP	104	24 (23.1)	106	39 (36.8)	−13.7	(−26.0 to −1.5)
HAP, mechanically ventilated	69	21 (30.4)	70	19 (27.1)	3.3	(−11.8 to 18.3)
Clinically evaluable						
All patients	251	174 (69.3)	244	174 (71.3)	−2.0	(−10.0 to 6.1)
HAP (excluding VAP)	198	154 (77.8)	185	141 (76.2)	1.6	(−6.9 to 10.0)
VAP	53	20 (37.7)	59	33 (55.9)	−18.2	(−36.4 to −.0)
HAP (excluding VAP), mechanically ventilated	38	21 (55.3)	37	15 (40.5)	14.7	(−7.6 to 37.1)

- Cephalosporin with activity MRSA
- Pre-clinical PK-PD (mouse)
  T>MIC 25% = ↓2 log CFU/g in lung
- Mice plasma exposure ≈ lung exposure
- Phase I and II PK (serum PK)
  Ceftobiprole 0.5g q8h 2h infusion = *f*T>MIC 50% and 60% for Gram+ve and –ve pathogens, respectively[2]

Why did it fail to show superiority?

- **Lung penetration different between mice and humans**

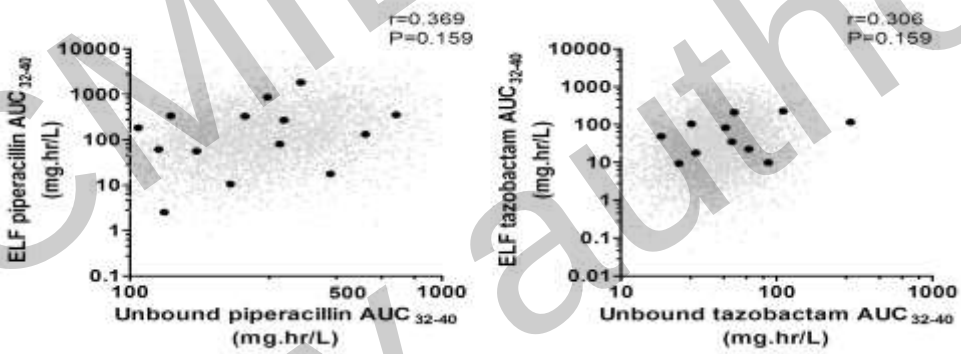
Median AUC_{ELF} :AUC_{serum} was 15.3 % (vs 69% in mice)[1]

- **PK variability: VAP patients > volunteers**

1. Rodvold KA et al. AAC.2009; 53(8):3294-3301. 2. Lodise TP et a. AAC.2007; 51(7):2378-87

ELF Studies in humans: β Lactams (%T>MIC)

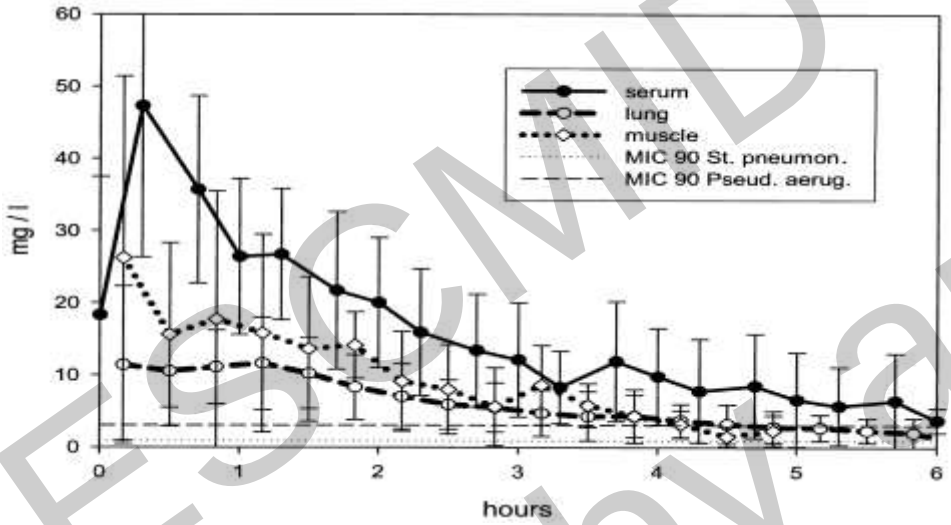
- Critically ill patients with nosocomial pneumonia (n=17) , standard bolus regimen (4 /0.5 g q8 h) and NBL: median penetration ratios of 49.3 % for **piperacillin** and 121.2% for **tazobactam**
- Intra-pulmonary **piperacillin-tazobactam** exposures are highly variable and unrelated to plasma



Felton TW et al Clin Pharm Ther 2014 96(4) 438-48

ELF Studies in humans: β-Lactams

- Penetration of **meropenem** in infected lung interstitial fluid tissue based on microdyalisis (after the fifth IV adm of 1 g 20 min infusion) in patients (n=7) with empyema undergoing decortication (40 ± 20%), % T> MIC= 80 (6 hours)

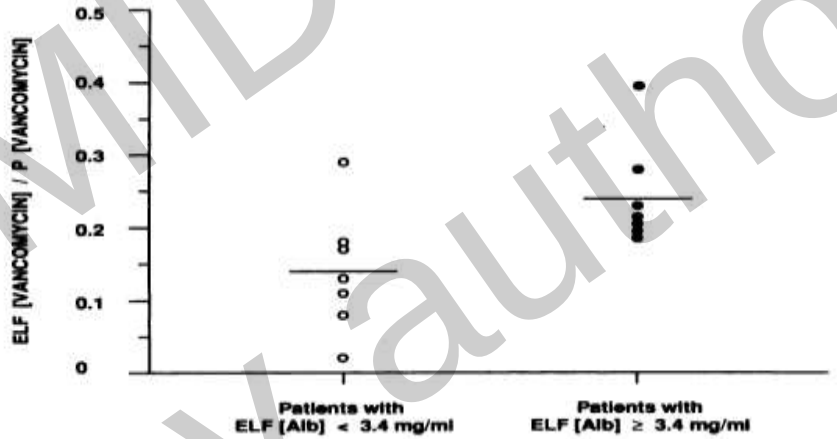


- **Is this method feasible to apply to larger number of patients in clinical trials?**
- **Can we use concentrations in muscle as a surrogate?**

Florian Tomaselli et al. Antimicrob. Agents Chemother. 2004;48:2228-2232

ELF Studies in humans: Glycopeptides (AUC/MIC)

- **Vancomycin** in critically ill patients with VAP (n=14) showed a mean penetration rate of 20%. Albumin $_{ELF}$ as a marker of inflammation. Sampling at a simultaneous single time-point: **System hysteresis**



Lamer C et al. AAC 1993; 37(22): 281-6

PK-PD studies of pneumonia related to clinical outcomes

- A) Serum drug concentrations
- B) ELF drug concentrations
- Do ELF PK-PD targets correlate with clinical outcomes in patients with nosocomial pneumonia?
- Literature Search: Pubmed (Medline), Scopus and Clinical Trials.gov databases, Mesh terms: “pharmacodynamics” AND “bacterial pneumonia” AND “clinical outcomes”
- 483 articles, only 10 eligible for A; 0 for B

PK-PD studies of pneumonia related to clinical outcomes

- **A) Serum drug concentrations**

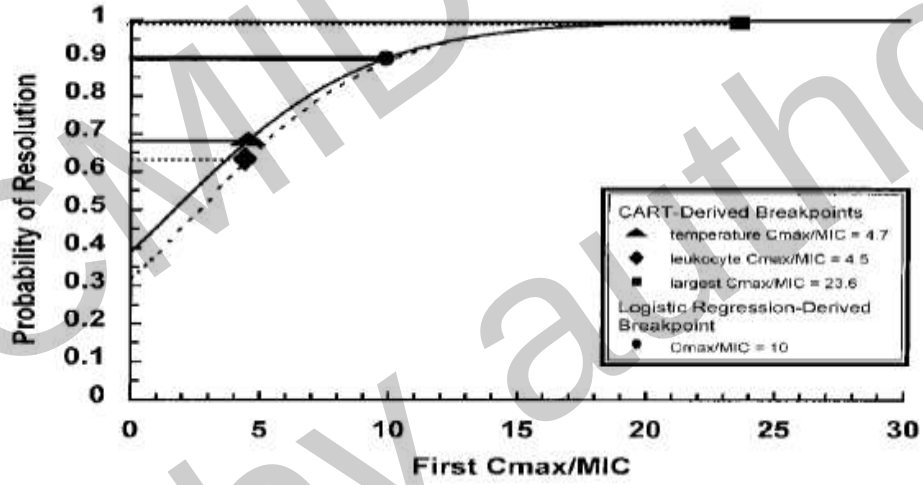
1) **Vancomycin AUC/MIC ≥ 400** predicts time-related **clinical and bacteriological** outcomes in patients with LRTI caused by MRSA[1]
2) **Carbapenems and piperacillin-tazobactam** extended (≥3 h) and Cont. (24h) infusions are associated with lower **mortality** in general and in patients with pneumonia[2]

1. Moise-Broder PA et al. Clin. Pharmacokinetics. 2004;43(13):925-42. 2. Falagas ME et al. CID 2013; 56(2):272-82

PK-PD studies of pneumonia related to clinical outcomes

- **A) Serum concentrations:**

3) Aminoglycosides (gentamycin/tobramycin)



Kashuba AD et al. AAC.1999; 43(3):623-29

PK-PD studies of pneumonia related to clinical outcomes

- **B) Plasma and ELF concentrations**
- **No studies to correlate ELF PK-PD indexes with clinical outcomes!!**
- **What are the challenges?**

1.- ELF PK-PD parameters and magnitude in mice might **not be the same** in humans

Comparison of pre-clinical and clinical pharmacodynamics (serum)

	Pre-clinical studies Maximum killing	**Clinical studies** Microbiological cure
Penicillins	50% T>MIC	50% T>MIC
Carbapenems	40% T>MIC	54% T>MIC
Fluoroquinolones	AUC/MIC > 30-100	AUC/MIC > 34-125

Roberts et al. Lancet Infect Dis 2014. 14: 498–509

Challenges of PK-PD clinical studies (ELF concentrations)

2.- Extent of Variability: differing ELF penetration ratios by/within drug class and at the individual level (inter- and intra-patient): severity of lung disease, underlying disease…

3.- Multiple and informative ELF sampling in patients

4.- Emergence of drug resistance under-studied *in vivo* and at the site of infection: a) Consider a combination of PK-PD parameters concentration e.g AUC/MIC and Cmax/MIC

b) Increased magnitude of target if MIC increases (risk of toxicity)

Recent examples of “failures” in drug development for pneumonia (serum)

- Daptomycin: Failed trial in CABP (binding to surfactant)[1,2]
- Doripenem: Higher mortality and lower cure rates in VABP[3]
- Tigecycline: Higher mortality and lower cure rates in VABP [4]
- Ceftobiprole: Lower cure rates in VABP[5]

1. Silverman JA et al. J Infect Dis. 2005. 2.Pertel P et al. CID 2008; 3. Kollef MH et al. Crit Care 2012;
4. Freire AT et al. Diag Microb and Infect Dis 2010; 5. Award S et al. CID 2014

Future research

- Novel strategies for individualized TDM and therapy are needed (dual output control: drug concentrations and PD endpoint)
- Improved methods to measure and monitor ELF concentrations in patients/ surrogate tissues (skeletal muscle?)
- Investigation of more disease-specific clinical/PD endpoints as well as CRP, PCT, bacterial burden markers…rather than mortality
- Investigation of emergence of resistance suppression strategies during therapy: 1) Continuous pre-clinical challenge of dosing regimens using *in vitro* models of infection (HFIM) to investigate the suppression of resistance 2) evaluation of the impact *in vivo*?

Conclusions

1. The extent and rate of penetration into ELF differs significantly by and within drug class
2. ELF studies in patients should be conducted before the selection of dosing regimens for HAP and VAP studies : high variability
3. There is no evidence that confirms whether ELF exposure rather than plasma is more predictive of outcome in patients with pneumonia
4. If this is the case, then measurements in the pulmonary compartment and adaptive methods of individualized regimens (TDM strategies) may be required

Thanks for your attention!
Questions?

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TABLE 3. INITIAL EMPIRIC ANTIBIOTIC THERAPY FOR HOSPITAL-ACQUIRED PNEUMONIA OR VENTILATOR-ASSOCIATED PNEUMONIA IN PATIENTS WITH NO KNOWN RISK FACTORS FOR MULTIDRUG-RESISTANT PATHOGENS, EARLY ONSET, AND ANY DISEASE SEVERITY

Potential Pathogen	Recommended Antibiotic*
Streptococcus pneumoniae†	Ceftriaxone
Haemophilus influenzae	*or*
Methicillin-sensitive *Staphylococcus aureus*	Levofloxacin, moxifloxacin, or ciprofloxacin
Antibiotic-sensitive enteric gram-negative bacilli	*or*
Escherichia coli	Ampicillin/sulbactam
Klebsiella pneumoniae	*or*
Enterobacter species	Ertapenem
Proteus species	
Serratia marcescens	

* *See* Table 5 for proper initial doses of antibiotics.

† The frequency of penicillin-resistant *S. pneumoniae* and multidrug-resistant *S. pneumoniae* is increasing; levofloxacin or moxifloxacin are preferred to ciprofloxacin and the role of other new quinolones, such as gatifloxacin, has not been established.

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‡