

# MONTE CARLO SIMULATION & PK-PD TARGET ATTAINMENT ANALYSIS:

## *Application to Oral Time-Dependent Antimicrobial Regimens*

Paul G. Ambrose, Pharm.D.

Director, Division of Infectious Diseases, Cognigen Corporation;  
Adjunct Professor, University of the Pacific, School of Health Sciences

# ACKNOWLEDGEMENTS

## Co-Authors:

**SUJATA M. BHAVNANI , PHARM.D.**

*Cognigen Corp., Buffalo, N.Y.*

**CHRIS M. RUBINO, PHARM.D.**

*Cognigen Corp., Buffalo, N.Y.*

**LUANN PHILLIPS, MBMA**

*Cognigen Corp., Buffalo, N.Y.*

## Sponsor:

**FUNDED, IN PART, BY A GRANT FROM:**

*Bayer Corporation*

# BACKGROUND

## *Monte Carlo Simulation*

- Introduced to the PK-PD community of practice in 1998 by Drusano (FDA Subcommittee on Anti-infective Drug Products).
- Has been used for evaluating antibiotic regimens for which outcome is best described by either AUC:MIC Ratio (PO or IV) and T>MIC (IV)
- We utilized an approach that may be useful to estimate the probability of attaining a given T>MIC for oral, time-dependent antibiotics
  - ◆ Amoxicillin-clavulanate
  - ◆ 500mg every 8 hrs versus 875mg every 12 hrs

# AMOXICILLIN-CLAVULANATE

## *Why Should Anyone Care?*

- Few drugs are available for clinical use in the community setting with reliable activity against *Streptococcus pneumoniae*
- 500mg Q8hrs vs. 875mg Q12hrs is a relevant comparison because patients are markedly more compliant on twice-daily regimens
- Given the limited therapeutic alternatives and the prevalence of multi-drug resistant pneumococci, it is important to demonstrate similar probabilities of PK-PD target attainment

# METHODS

## *Monte Carlo Simulations*

- Simulations considered *Streptococcus pneumoniae* and *Haemophilus influenzae* collected in the U.S. and Europe
- Simulations also considered potential MIC breakpoints
- 10,000 patient simulation for each drug-organism or -fixed MIC value combination
- In order to account for clavulanate exposure, important for efficacy against beta-lactamase producing strains of *H. influenzae*, a 2-step algorithm was used
- $T > MIC$  was computed numerically using the bisection method for finding roots of equations

# METHODS

## *Simulation Assumptions*

- One-compartment pharmacokinetic data for amoxicillin/amoxicillin-clavulanate was obtained from the medical literature and utilized for the purpose of simulation

	Amoxicillin [Mean (%CV)]		Clavulanate [Mean (%CV)]
	500 mg	875 mg	125 mg
$K_a$ (1/hr)	1.48 (14.2)	1.49 (28.7)	2.80 (32.5)
$K_e$ (1/hr)	0.762 (15.5)	0.791(23.3)	0.972 (7.8)
CL (L/hr)	24.5 (12.2)	24.7 (19.5)	15.6 (12.5)
$f_u$	0.82	0.82	0.80

Aguilar L, et al. Antimicrob Agents Chemother 1998;41:1389-1391.

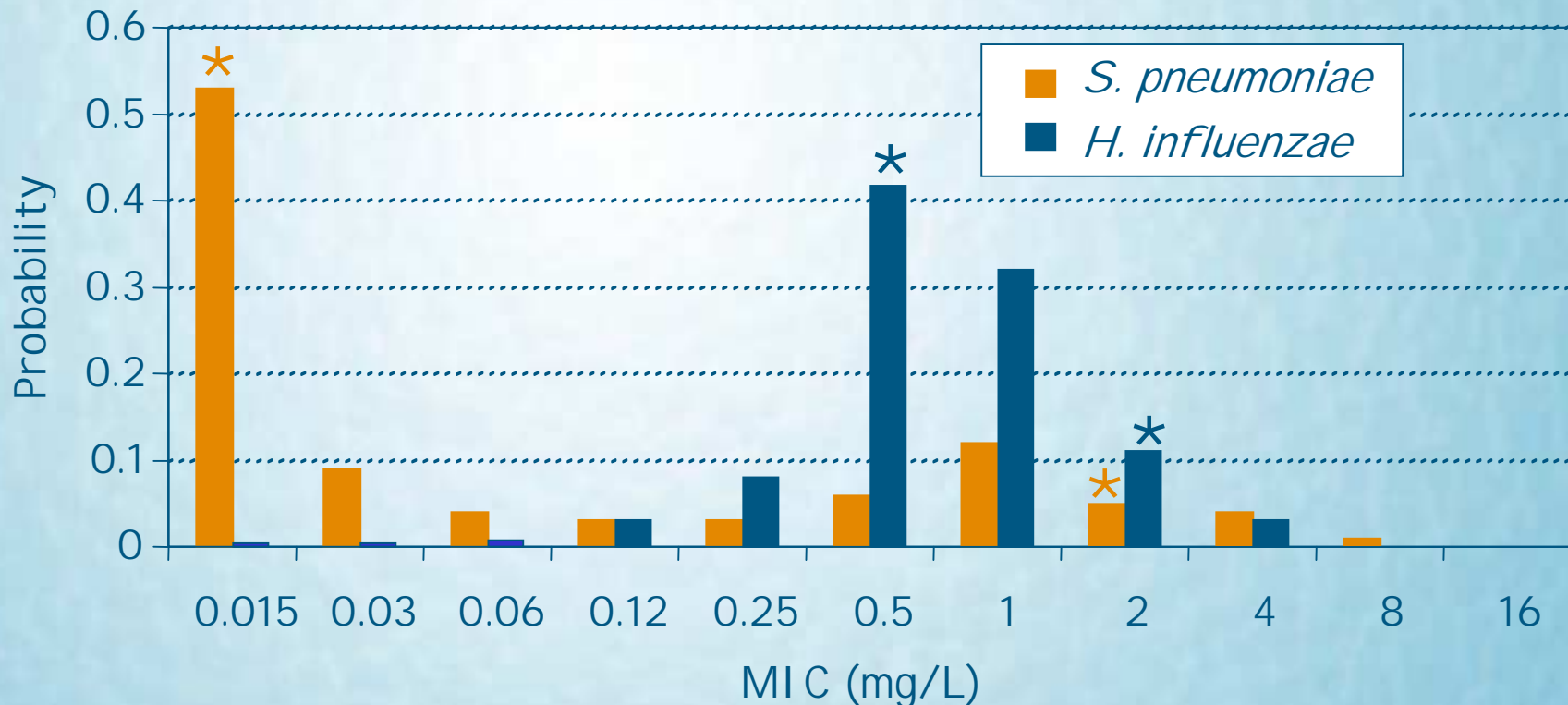
Aranciba A, et al. International J Clin Pharmacol Ther Toxicol 1988;26:300-303.

Adam D, et al. Antimicrob Agents Chemother 1982;22:353-357.

# METHODS

## *Amoxicillin-Clavulanate MIC Distribution*

- 4,725 isolates of *S. pneumoniae* & 2,505 isolates of *H. influenzae* collected in the United States (1999-2000)

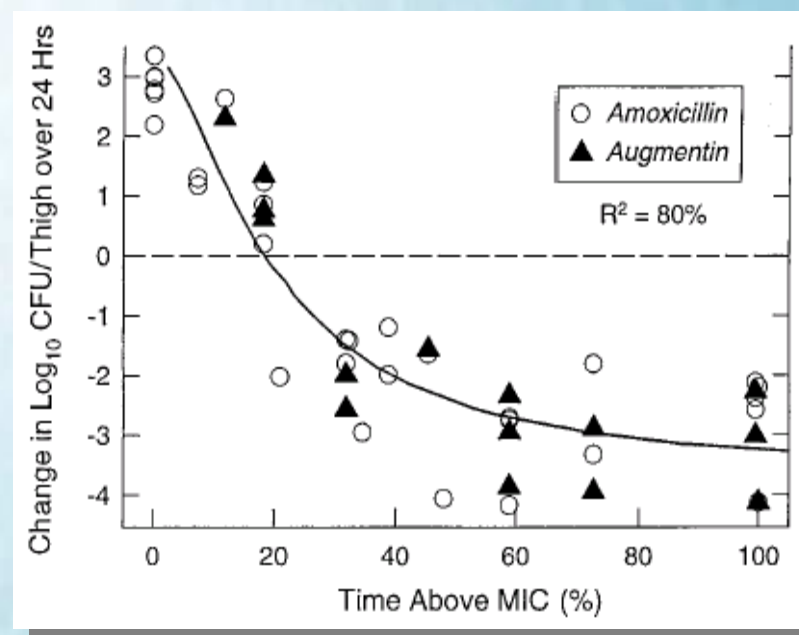
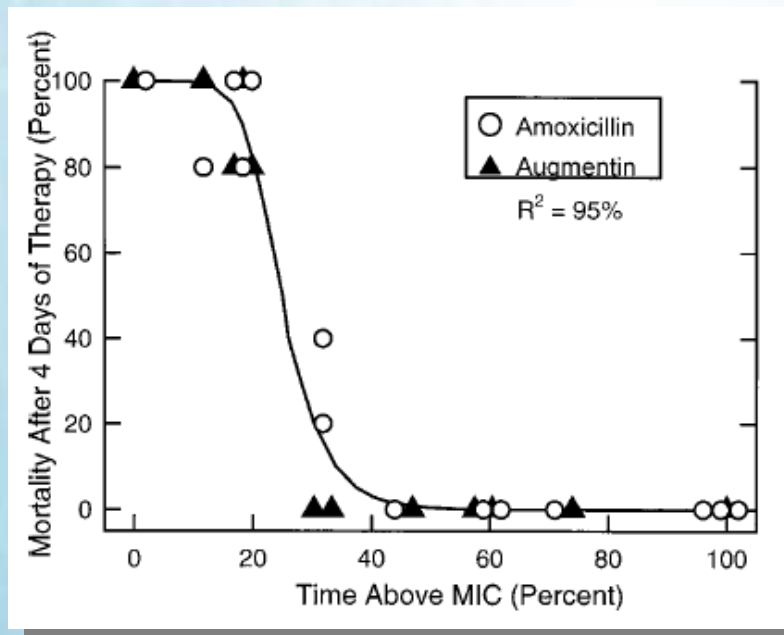


I.A. Critchley, J.A. Karlowsky, D.C. Draghi, M.E. Jones, C. Thornsberry, K. Murfitt, D.F. Sahm. Activity of faropenem, an oral carbapenem, against recent U.S. isolates of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Antimicrob Agents Chemother 2002 46(2): 550-5.

# AMOXICILLIN-CLAVULANATE

## *PK-PD Goal of Therapy for S. pneumoniae*

- Mice rendered neutropenic & infection induced by IM injection of 0.1mL of  $10^5$  to  $10^6$  CFU *S. pneumoniae*
- Animals received 7 mg/kg alone or in combination with clavulanate (ratio 4:1) every 8 hrs.
- Each data point represents the mean of two thighs.



Andes D, Craig WA. In vivo activities of amoxicillin and amoxicillin-clavulanate against *Streptococcus pneumoniae*: Application to breakpoint determination. *Antimicrob Agents Chemother* 1998;42:2375-2379.

# SIMULATION RESULTS: *S. pneumoniae*

## *Amoxicillin-Clavulanate (500-125mg Q8hr Regimen)*

MIC	PK-PD TARGET (T>MIC)				
	25%	30%	35%	40%	
0.12	100	100	100	100	S
0.25	100	100	100	100	
0.5	100	100	100	100	
1.0	100	100	100	100	
2.0	100	100	99.9	98.7	
4.0	99.7	95.4	63.2	17.4	I
8.0	10.0	0.7	0.0	0.0	R
Entire MIC Distribution	99.1	98.7	97.2	95.7	
PCN-S	100	100	100	100	
PCN-I	100	100	99.6	98.5	
PCN-R	98.5	87.7	76.5	62.1	

# SIMULATION RESULTS: *S. pneumoniae*

## *Amoxicillin-Clavulanate (875-125mg Q12hr Regimen)*

MIC	PK-PD TARGET (T>MIC)				
	25%	30%	35%	40%	
0.12	100	100	99.8	99.3	S
0.25	100	99.8	99.3	96.9	
0.5	99.8	99.3	96.4	91.8	
1.0	99.3	95.9	90.5	79.3	
2.0	95.2	87.2	71.5	50.6	
4.0	80.7	56.9	37.1	20.4	I
8.0	36.3	19.5	8.5	3.3	R
Entire MIC Distribution	99.7	96.1	93.3	90.4	
PCN-S	100	100	100	99.9	
PCN-I	99.1	96.2	92.3	84.7	
PCN-R	85.6	71.0	56.7	44.6	

# SIMULATION RESULTS: *H. influenzae* Amoxicillin-Clavulanate

Dose	MIC Distribution	n	PK-PD TARGET (T>MIC)			
			25%	30%	35%	40%
500-125 mg Q8 hr	Entire	2505	99.9	99.9	99.8	98.7
	BL-	1645	100	100	99.9	98.3
	BL+	860	99.9	99.8	99.5	99.5
875-125 mg Q12 hr	Entire	2505	98.2	97.5	95.9	93.5
	BL-	1645	99.7	98.9	97.7	94.9
	BL+	860	95.2	94.8	92.3	90.8

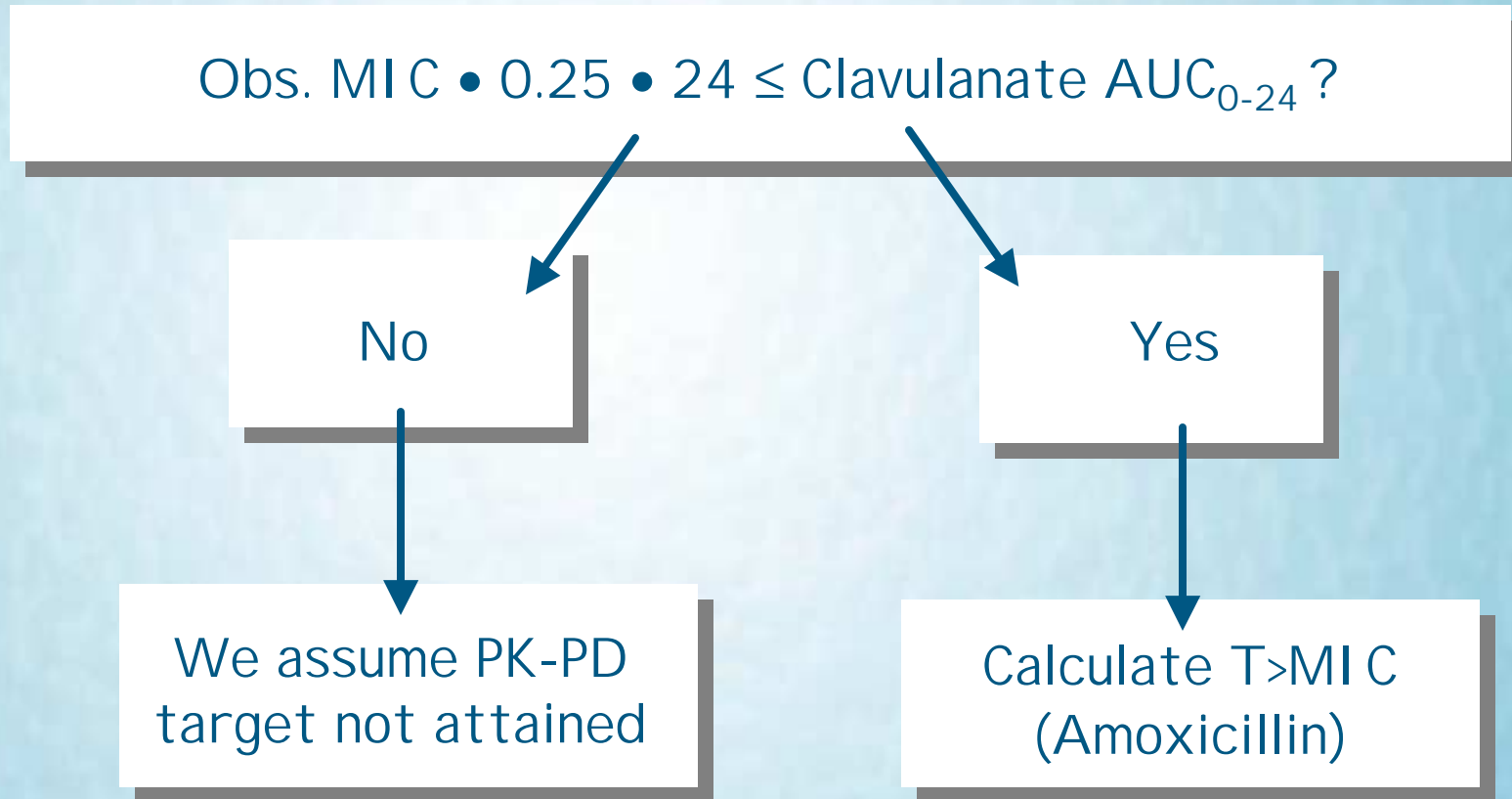
# CONCLUSIONS

- The bisection method is useful for PK-PD target analyses for oral, time-dependent antimicrobial agents
- From PK-PD perspective, the 875 mg amoxicillin-clavulanate regimen Q12 hr is generally comparable to 500 mg Q8 hr amoxicillin-clavulanate regimen
- These data suggest that the current NCCLS breakpoints for amoxicillin against *S. pneumoniae* of 2, 4 and 8 mg/L for susceptible, intermediate and resistant, respectively, are reasonable

QUESTIONS, COMMENTS OR  
WISE REMARKS?

# BACK-UP METHODS

## *2-Step Algorithm*



Dudley MN. Combination beta-lactam and beta-lactam-inhibitor therapy pharmacokinetic and pharmacodynamic considerations. Am J Health-Syst Pharm 1995;52(suppl 2):23-28

Jones RN, Dudley MN. Microbiologic and pharmacodynamic principles applied to the antimicrobial susceptibility testing of ampicillin/sulbactam. Diagn Microbiol Infect Dis 1997;28:1-14.

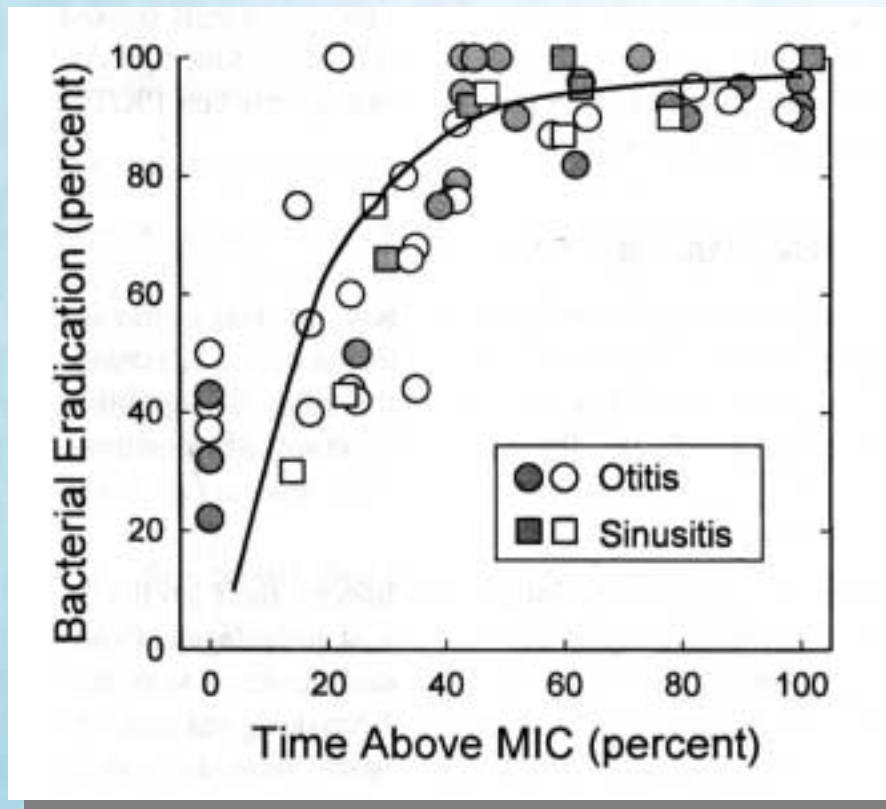
# BACK-UP METHODS

## *2-Step Algorithm*

- Since the clavulanate component is critical to activity of amoxicillin-clavulanate against *H. influenzae*, we considered a 2-step algorithm
  - ◆ Susceptibility testing of *H. influenzae* uses a fixed ratio of 4:1 amoxicillin:clavulanate
  - ◆ Approximately 97% of *H. influenzae* strains had MIC values of  $\leq 2$  mg/L
  - ◆ A MIC value of 2 mg/mL may be thought of as a clavulanate  $AUC_{24}$  of 12
  - ◆ Since the mean and std. dev. of clavulanate  $AUC_{24}$  was  $19.2 \pm 2.4$ , in >99% (3 Std. Dev.) of the instances the  $AUC_{24}$  in subjects would be expected to be 12 or greater .
  - ◆ Thus, in these simulations clavulanate exposure is sufficient in approximately at least 97% of all instances and the simulation largely simplifies to considering the amoxicillin component

# PK-PD Goal of Therapy $\beta$ -Lactams

*S. pneumoniae* & *H. influenzae*



- Data from AOM or ABRS studies
- Pre-therapy and repeat sinus puncture or tympanocentesis
- 40% T>MIC or greater required to achieve 85-100% bacteriologic cure for both organisms

Craig WA. Pharmacodynamics of antimicrobials: general concepts and applications. /n: Nightingale CH, Murakawa T, Ambrose PG ed. Antimicrobial Pharmacodynamics in Theory and Practice. New York, Marcel Dekker Publishers, 2002.

