The Medicines Company

Developing Combinations for Pneumonia: Indications, Regulation, and Opportunities

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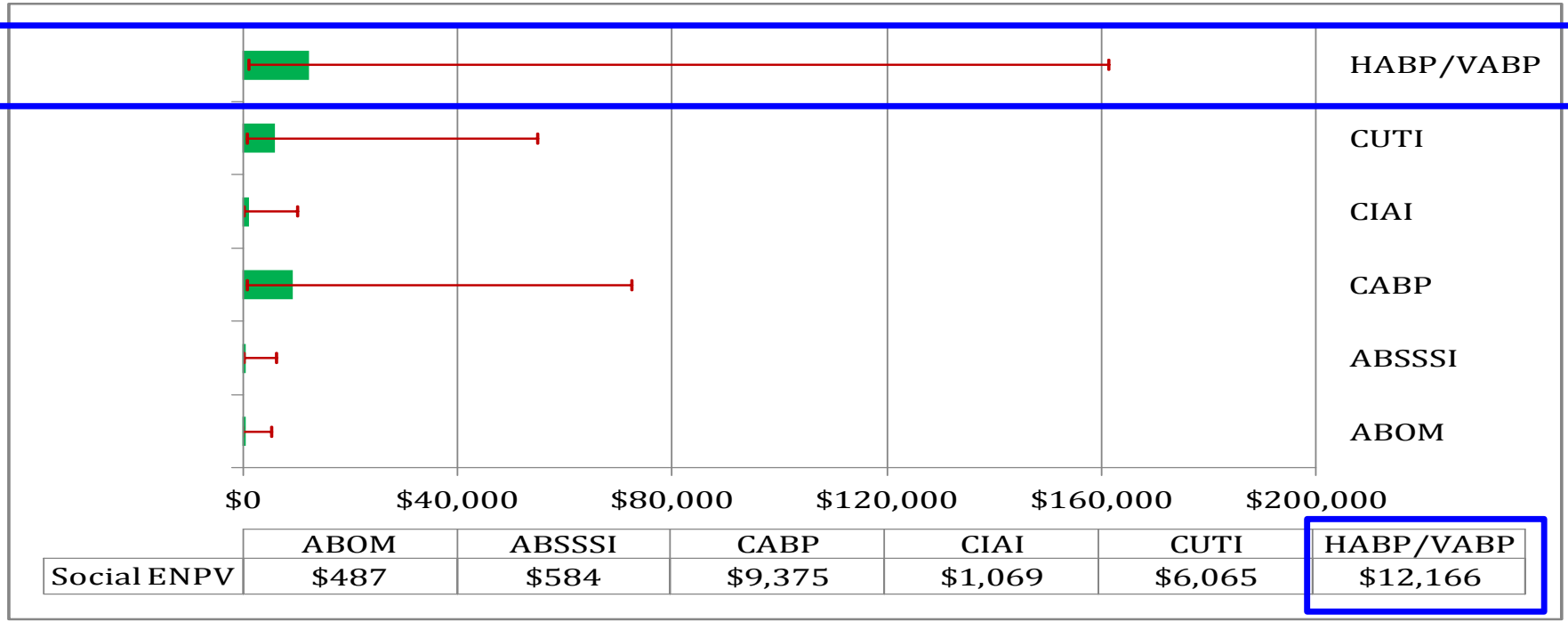
MN Dudley: Disclosure

- Employee, hold stock in the The Medicines Company
- Hold equity with the following: Rempex Pharmaceuticals, Tripex Pharmaceuticals
- Principal investigator for meropenem-vaborbactam program that is supported in part with federal funds from the Department of Health and Human Services; Office of the Assistant Secretary for Preparedness and Response; Biomedical Advanced Research and Development Authority (BARDA), under Contracts Nos. HHSO100201400002 and HHSO100201600026C
- Principal Investigator and Management Board member of the Innovative Medicines Initiative's (IMI) ND4BB COMBACTE-NET program in the EU
- Special thanks to: Paul Ambrose/ICPD, FNIH, and CTTI
- Several investigational agents and potential uses will be discussed that are not approved by the US FDA

Outline

- Why study new drugs in HABP/VABP?
- Challenges in conducting studies of new drugs in HABP/VABP
- Collaborations between regulators, industry and clinical trial specialists are providing helpful guidance for design and conduct of feasible clinical trials
- PK and PK-PD considerations:
  - Lessons learned
  - Special considerations for fixed combination products (beta-lactam/beta-lactamase inhibitors)

Opportunities: Societal Estimated Net Present Value (ENPV) for Treatments That Improve Mortality, Morbidity and Avoid Delay in Clinical Response



	ABOM	ABSSSI	CABP	CIAI	CUTI	HABP/VABP
Social ENPV	$487	$584	$9,375	$1,069	$6,065	$12,166

*This analysis supports **early use of active antibiotics** in patients that would improve mortality/morbidity and avoiding delays in clinical response (ie, **use the active drugs first**) have the greatest **societal impact***

- *Eastern Research Group under contract from FDA and NIAID, 2014*

Unmet Need: No Drugs for Pulmonary Infections, Especially Nosocomial Pneumonia (HABP/VABP)

Number of Antibiotics with initial FDA approval(s) according to indication and year

	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Oral	1	2	2		1		1		1	1												
Oral & IV		1	1		1	1														1		
IV		1	1		1		1		1		1				1	1				3	1	
Mild RTI	3	3	4		4		2			2												
uSSTI		1	1				1															
uUTI		1			1				1													
Genital			2		2																	
CABP		2	3		2	1	1			1						1						
NP			1			1																
cSSTI			1		1	1	1		1		1				1	1				3		
cUTI		1	1		1		1													1	1	
cIAI		1	2				1				1									1	1	
Meningitis		1																				

!!!

- Rex JH, Talbot GH, Goldberger MJ, Eisenstein BI, Echols RM, Tomayko F, Dudley MN, Dane A. Progress in the Fight vs. MDR Bacteria 2005-16: Modern Noninferioty Trial Designs Enable Antibiotic Development in Advance of Epidemic Bacterial Resistance. Clin Infect Dis 2017 (online)

Challenges in Conducting Clinical Trials in HABP/VABP

- Feasibility: slow/difficult enrollment, extensive data collection
- Cost of trials
- PK, PK-PD Considerations and Perils in Clinical Trials

Per Patient Costs in a HABP/VABP Trial Are Among the Highest:

Comparisons With Oncology and Endocrine Clinical Trials

(*Stergiopoulos S, et. al. DIA 2016, poster T08)*

Therapeutic Area	Per-Patient Direct Cost ($000)	Per-Trial Direct Cost ($000)	Indirect Cost ($000)	Total Cost Per Patient ($000)
Endocrine	$9.5	$42.3	$5.8	**$57.5**
Oncology	$18.2	$61.8	$7.5	**$87.4**
HABP/VABP*	$66.1	$20.1	$3.3	**$89.6**

- Key Driver of Cost in HABP/VABP in Per Patient Direct Costs
  - Recruitment/consenting process
  - Screen failures: Cost as well as screen failure rate
  - Trial size: requirement of more sites

Collaborations Between Expert Clinicians, Industry, and Regulators are Helping to Improve Trials in HABP/VABP

- Clinical Trials Transformation Initiative (CTTI; *Clin Infect Dis 2016 Suppl 2;* *https://www.ctti-clinicaltrials.org/projects/streamlining-habpvabp-trials*)
  - Streamlining protocol elements (e.g., improved informed consent procedures (pre-consent in high risk patients; protocol design; IRBs; outcomes/endpoints)
  - Operational efficiencies for data collection (AEs; lab data; con meds)
  - Prospective observational study of risk factors for HABP and VABP (CTTI 001)

- Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium
  - Assessment of the robustness of all cause mortality endpoint across various HABP/VABP patient subsets (e.g., ventilated HABP)
  - Prognostic factors
  - Alternative endpoints
  - PROs
  - Submitted to FDA docket for review in May 2017

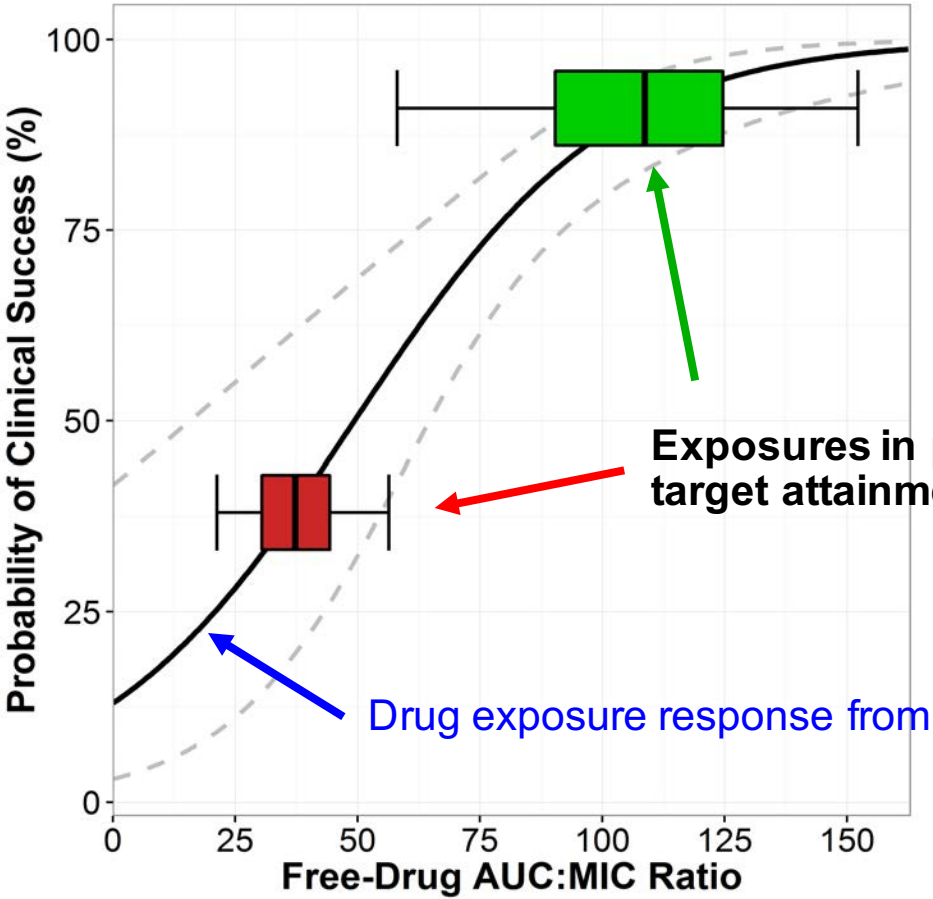
Recent Experience in Clinical Trials in HABP/VABP of Some Agents Have Included Some Hard PK-PD Lessons

- Low doses/exposures of doripenem
- Low ELF exposures with ceftibiprole
- Differences in tigecycline clearance, MICs in HABP vs. VABP

FDA Workshop, July 2016.
Slide/Analysis Courtesy of Dr. Paul Ambrose/ICPD

Understanding Efficacy in Clinical Trials:

Its all about where you are on the exposure-response curve

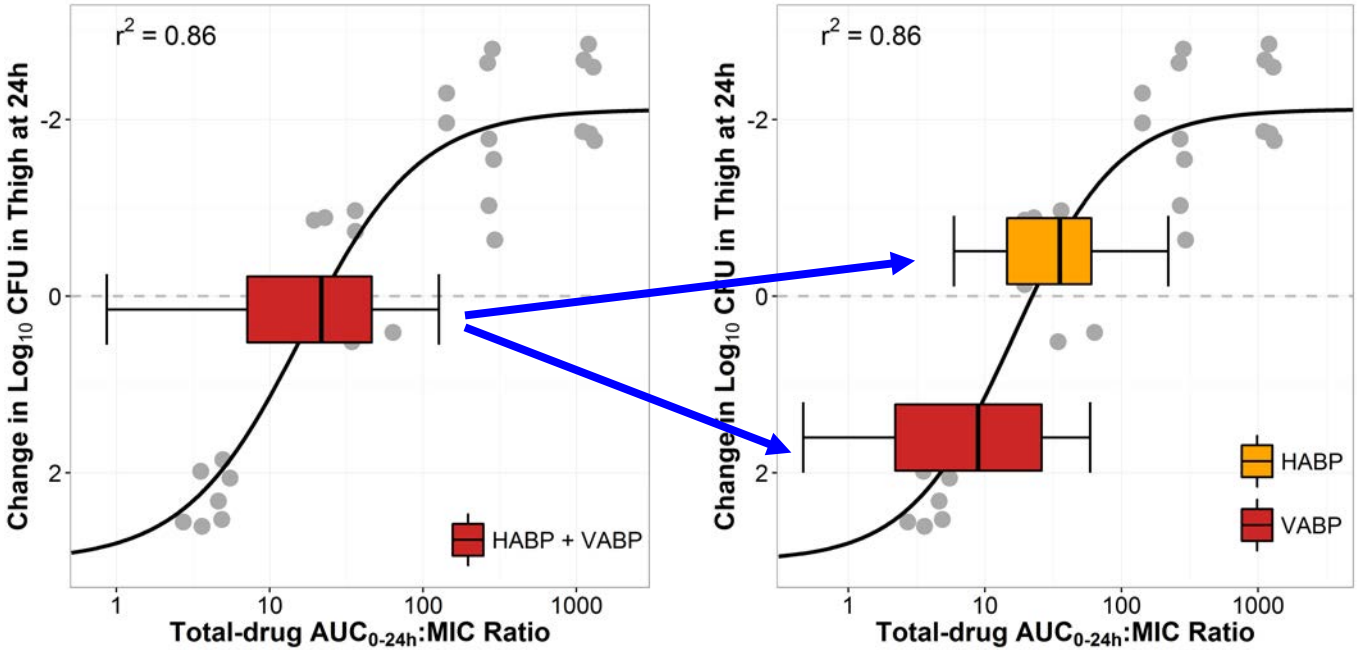


Exposures in patients linked with MIC distributions for target attainment estimates from simulations

Drug exposure response from nonclinical models of infection

FDA Workshop, July 2016. Slide/Analysis Courtesy of Dr. Paul Ambrose/ICPD

Marginal Dosing of Tigecycline, Higher Clearance in VABP Patients, and Higher MICs in VABP Patients Resulted in Poor Response



- Poor clinical results in VABP patients (Friere et. al, DMID 2010)
  - Population PK studies showed that tigecycline clearance was more rapid in patients with VABP
  - Higher MICs in VABP patients
  - The net impact is a downward shift to bottom of the dose response curve

Preclinical data: Courtesy of William A. Craig

Clinical data: Bhavnani SM, Rubino CM, Hammel JP, Forrest A, Dukart G, Dartois N, Cooper A, Korth-Bradley J, Ambrose PG. Pharmacological and patient-specific response determinants in patients with hospital-acquired pneumonia treated with tigecycline. *Antimicrob Agents Chemother.* 2012; 56:1065-1072

Rubino CM, Ma L, Bhavnani SM, Korth-Bradley J, Speth J, Ellis-Grosse E, Rodvold KR, Ambrose PG, Drusano, GL. Evaluation of tigecycline penetration into colon wall tissue and epithelial lining fluid using a population pharmacokinetic model and Monte Carlo simulation. *Antimicrob Agents Chemother,* 2007 November; *51*(11), 4085-4089.

FDA Workshop, July 2016. Slide/Analysis Courtesy of Dr. Paul Ambrose/ICPD

Combination Antimicrobial Therapy in HABP/VABP:
Special Case of Beta-lactam/Beta-lactamase Inhibitors

PK

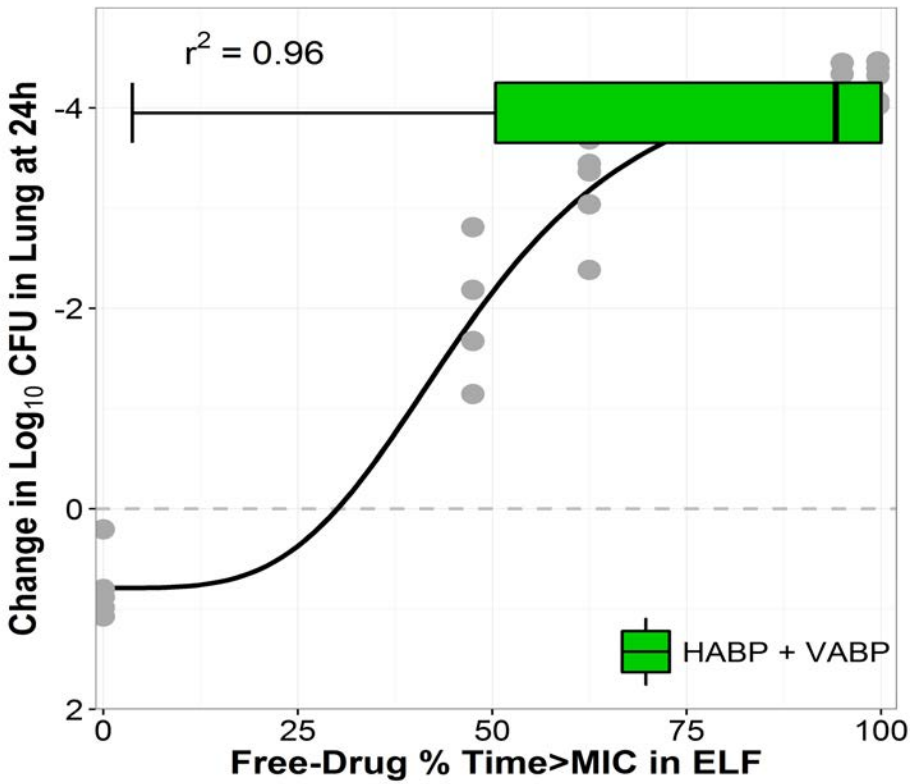
- Importance of PK of BOTH BLI and partner beta-lactam:
  - PK in ELF
  - PK in patients (renal impairment)

PK-PD

- Identify the PK-PD index for efficacy of a beta-lactamase inhibitor for bacterial killing AND resistance prevention
- Dosage regimens to insure you get those exposures in patients and with dosage adjustments in renal impairment

Meropenem PK-PD in Preclinical Models, PK in ELF and Patients

FDA Workshop, July 2016.
Slide/Analysis Courtesy of
Dr. Paul Ambrose/ICPD



Preclinical data: Louie A, Liu W, Fikes S, Brown D, Drusano GL. Impact of meropenem in combination with tobramycin in a murine model of *Pseudomonas aeruginosa* pneumonia. *Antimicrob Agents Chemother*. 2013 June; 57(6), 2788-2792.

Surveillance data: EUCAST (2016).MIC distributions and ECOFFs. Available at www.eucast.org/mic_distributions_and_ecoffs/. Accessed July 2016.

Clinical data: Mattioli F, Fucile C, Del Bono V, Marini V, Parisini A, Molin A, Zuccoli ML, Milano G, Danesi R, Marchese A, Polillo M, Viscoli C, Pelosi P, Martelli A, Di Paolo A. Population pharmacokinetics and probability of target attainment of meropenem in critically ill patients. *European journal of clinical pharmacology*, 2013;1-10.

Lodise TP, Sorgel F, Melnick D, Mason B, Kinzig M, Drusano GL. Penetration of meropenem into epithelial lining fluid of patients with ventilator-associated pneumonia. *Antimicrob Agents Chemother*. 2011 April; *55*(4), 1606-1610.

PK-PD of Meropenem plus the Beta-Lactamase Inhibitor Vaborbactam in Nonclinical Models

(Griffith D et. al. Microbe 2017 Poster Session 341-AAID03 #193; Sunday)

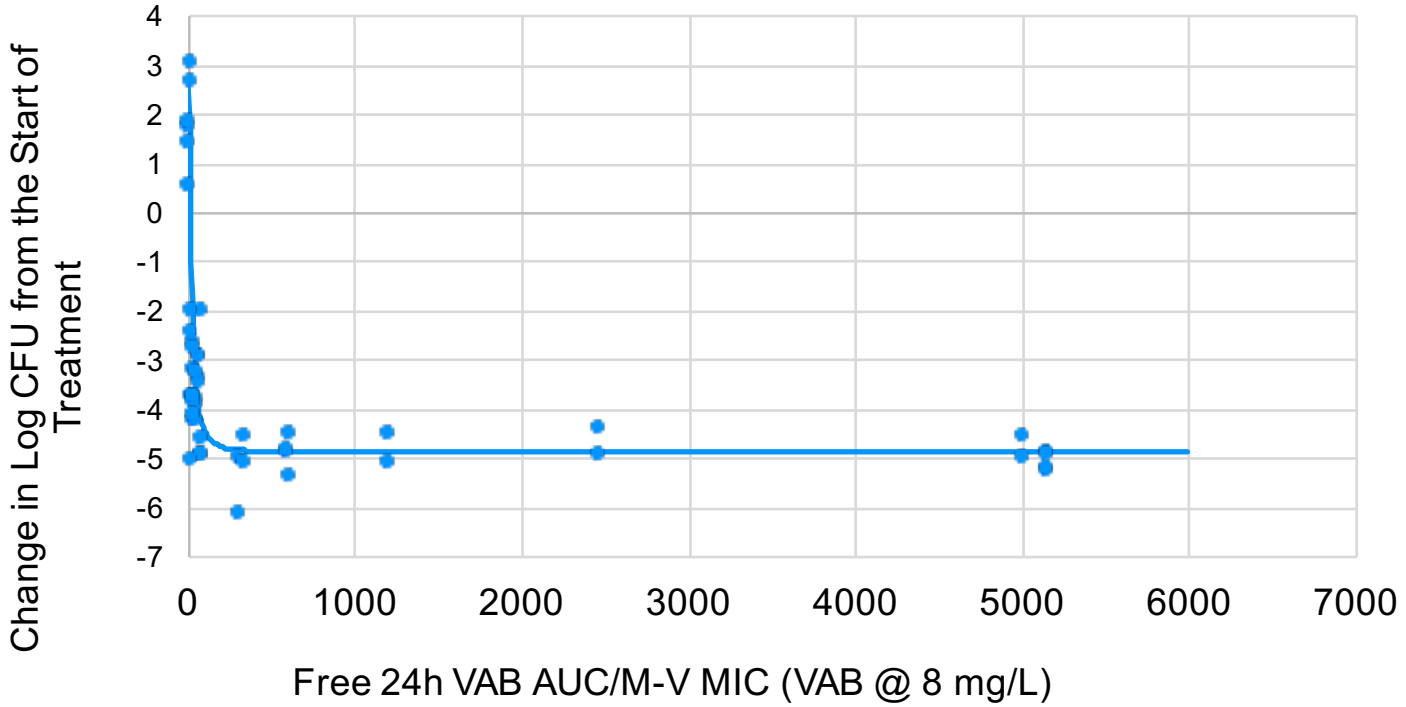
- KPC-containing strains of Enterobacteriaceae with meropenem-vaborbactam MICs ranging from 0.06 – 64 mg/L
- Selected from clinical isolates with mixtures beta-lactamases and other mutations known to affect sensitivity to meropenem and vaborbactam (e.g., OmpK mutations)
- Test high innocula (hollow fiber) to encourage resistance
- Identify PK-PD index for vaborbactam

Strain	Beta-Lactamases	OmpK35	OmpK36	Meropenem MIC (µg/mL)			Model
				Alone	w/Vaborbactam		
					4 µg/mL	8 µg/mL	
E. coli EC1007	KPC-3	ND	ND	8	≤0.06	≤0.06	HF
E. cloacae ECL1058	KPC-3, SHV-11, TEM-1	FL	FL	8	0.125	0.125	HF
E. cloacae ECL1061	KPC-3, Hyper AmpC Expression	FS aa#287	FL	16	0.125	0.125	HF
E. cloacae ECL1079	KPC-3	stop aa#60	stop aa#77	>64	32	8	Mouse, HF
K. pneumoniae KP1061	KPC-3, SHV-11, TEM-1	FS aa#42	FL	16	≤0.06	≤0.06	HF
K. pneumoniae KP1074	KPC-3, SHV-11, TEM-1	FS aa#42	GD	>64	1	0.5	HF
K. pneumoniae KP1087	KPC-2, CTX-M-15, SHV-11, TEM-1	FS aa#208	GD	32	0.5	0.25	HF
K. pneumoniae KP1092	KPC-2, SHV-11, SHV-12, TEM-1	FS aa#42	IS at -45	>64	128	32	HF
K. pneumoniae KP1093	KPC-3, SHV-11, TEM	FS aa#42	GD	>64	2	0.5	Mouse, HF
K. pneumoniae KP1094	KPC-2, TEM-1, LEN-17	stop aa#230	stop aa#92	>64	32	4	Mouse, HF
K. pneumoniae KP1096	KPC-2, TEM, SHV-11	L63V, E132K	IS at nt#126	>64	64	16	Mouse, HF
K. pneumoniae KP1099	KPC-2, SHV-11, SHV-12, CTX-M-14	FS aa#29	GD	>64	4	1	HF
K. pneumoniae KP1100	KPC-3, TEM, SHV	FS aa#42	GD	>64	16	4	HF
K. pneumoniae KP1194	KPC-2 TEM SHV	FS aa#42	IS at -45	>64	64	8	HF
K. pneumoniae KP1223	KPC-2, SHV, TEM	FS aa#29	GD	>64	64	8	Mouse, HF
K. pneumoniae KP1244	KPC-3, SHV-11, SHV-12	FS aa#42	R191L, T333N	>64	64	16	HF
K. pneumoniae KP1254	KPC-2, SHV, TEM, OXA-10	FS aa#42	IS and ΔopmK36	>64	>64	64	HF

Meropenem-Vaborbactam PK-PD in Hollow Fiber Model

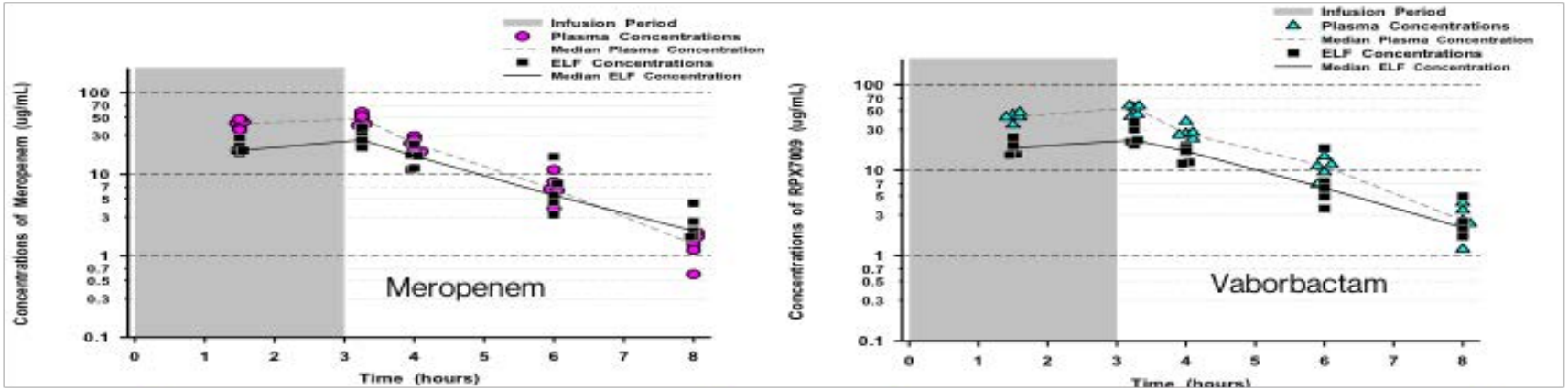
(Griffith D et. al. Microbe 2017 Poster Session 341-AAID03 #193; Sunday)

- KPC-producing strains of Enterobacteriaceae with meropenem-vaborbactam MICs ranging from 0.06 – 64 mg/L
- 24h free vaborbactam AUC:MIC m-v best describes bacterial killing in hollow fiber model
- Log kill and non beta-lactamase mediated resistance targets identified



Pharmacokinetics of Meropenem and Vaborbactam in Epithelial Lining Fluid (ELF) in Normal Subjects

Plasma and ELF concentrations at steady-state for meropenem 2g / vaborbactam 2g every 8 hrs as a 3hr infusion



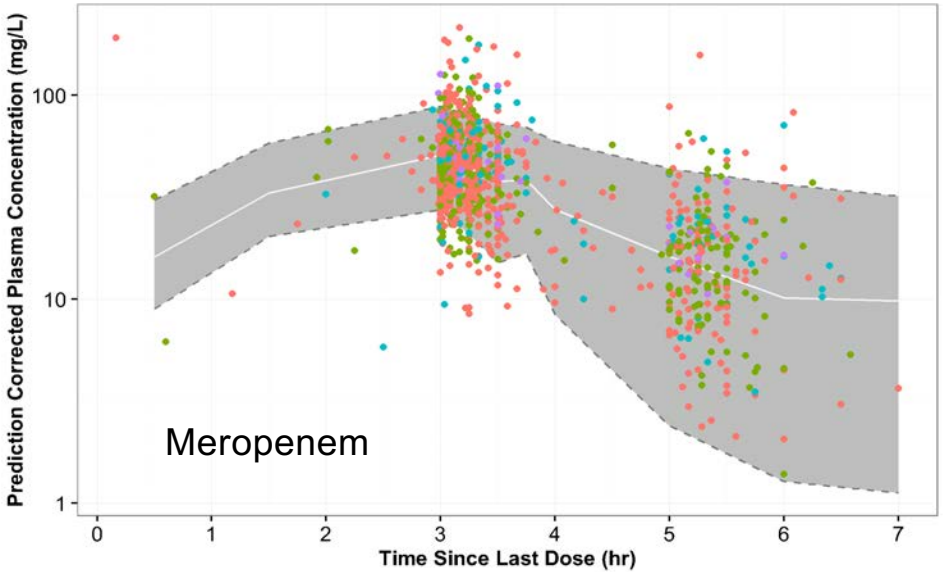
Meropenem AUC (ug-h/mL)			
	ELF	Plasma	E-P Ratio
Mean:	111.7	176.2	63%
Median:	102.4	176.8	58%

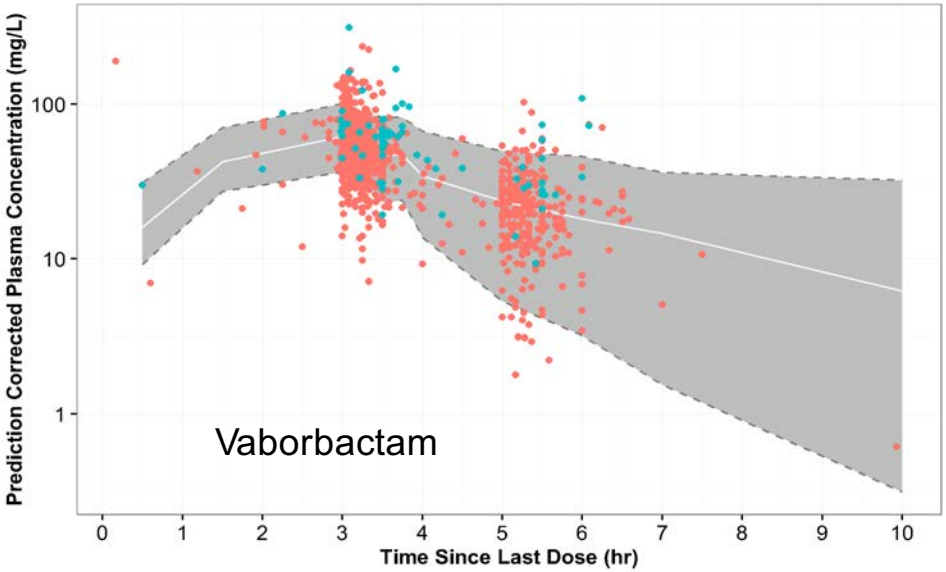
Vaborbactam AUC (ug-h/mL)			
	ELF	Plasma	E-P Ratio
Mean:	105.1	197.4	53%
Median:	96.7	199.9	48%

SOURCE: Wenzler et. al. Antimicrob Agents Chemother 2015;50;7232-9

Meropenem-Vaborbactam Population Pharmacokinetics in Healthy Volunteers and Infected Patients

(Trang et. al, Microbe 2017 Poster Session 341-AAID03 #192; Sunday)





Summary

- There is an unmet need for new drugs in HABP/VABP, especially with activity against MDR gram-negative pathogens
- Recent guidance and ongoing improvements in trial conduct and design are helping make them more feasible
- Clinical trial misadventures stemming from failure to consider pharmacometric relationships in the planning of trials
- Complexity is increased with combinations of agents, but can be dealt with by careful planning