Planning and Executing a Carbapenem/ Beta-lactamase Inhibitor Program Focused on Treatment of KPC-Producing CRE

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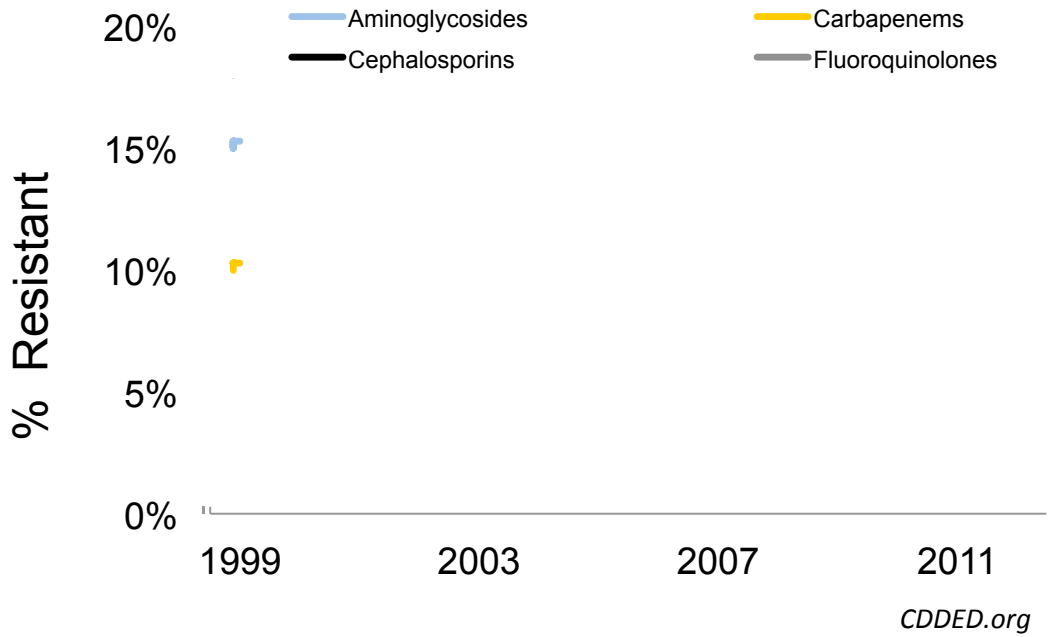
MN Dudley: Disclosure

- Employee of The Medicines Company
- Principal investigator of the meropenem/vaborbactam development program which is supported in part by 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 Contract No. HHSO100201400002

CRE:
a growing and urgent threat

- CDC threat category "Urgent"
- Rise of resistance
- High disease burden and mortality (20-50%)
- Limited treatment options

Antibiotic resistance in *Klebsiella pneumoniae* in the U.S.



- *Infect Cont Hosp Epidem*. 2013; 34(1):1-14
- Eurofins-TSN / CDDEP
- *Nat Rev Drug Discov.* 2013; Dec; 12(12): 963
- EviMed Analysis of Premier Database
- Vital Signs: Carbapenem-Resistant Enterobacteriaceae. MMWR 2013;62:165-70.
- Alexander E et al. ICAAC 2015

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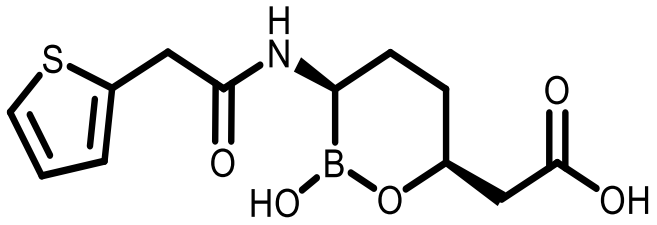
Vaborbactam:

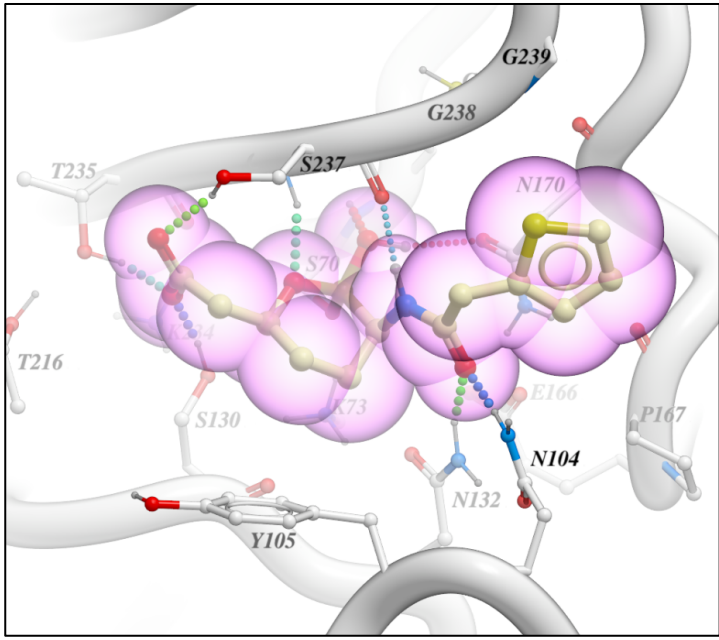
The First from a New Class of Beta-lactamase Inhibitors

Hecker et. al. J Med Chem 2015;58:3682-92

- New class of beta-lactamase inhibitor
  - Molecular modeling and medicinal chemistry identified a lead series of **cyclic boronic acid**
  - Potent inhibitory activity against Class A and C serine beta-lactamases, particularly the KPC carbapenemase
- Optimized for (1) **inhibition of serine carbapenemases**, and (2) **pharmacological** properties to combine with a **carbapenem**
- An accelerated development program focusing on a fixed combination product with meropenem was designed, with a **focus on KPC-producing CRE**
- Meropenem-vaborbactam advanced from the **chemist's benchtop through enrollment of a Phase 3 pivotal trial in just 6 years.**



Vaborbactam
(formerly known as RPX7009



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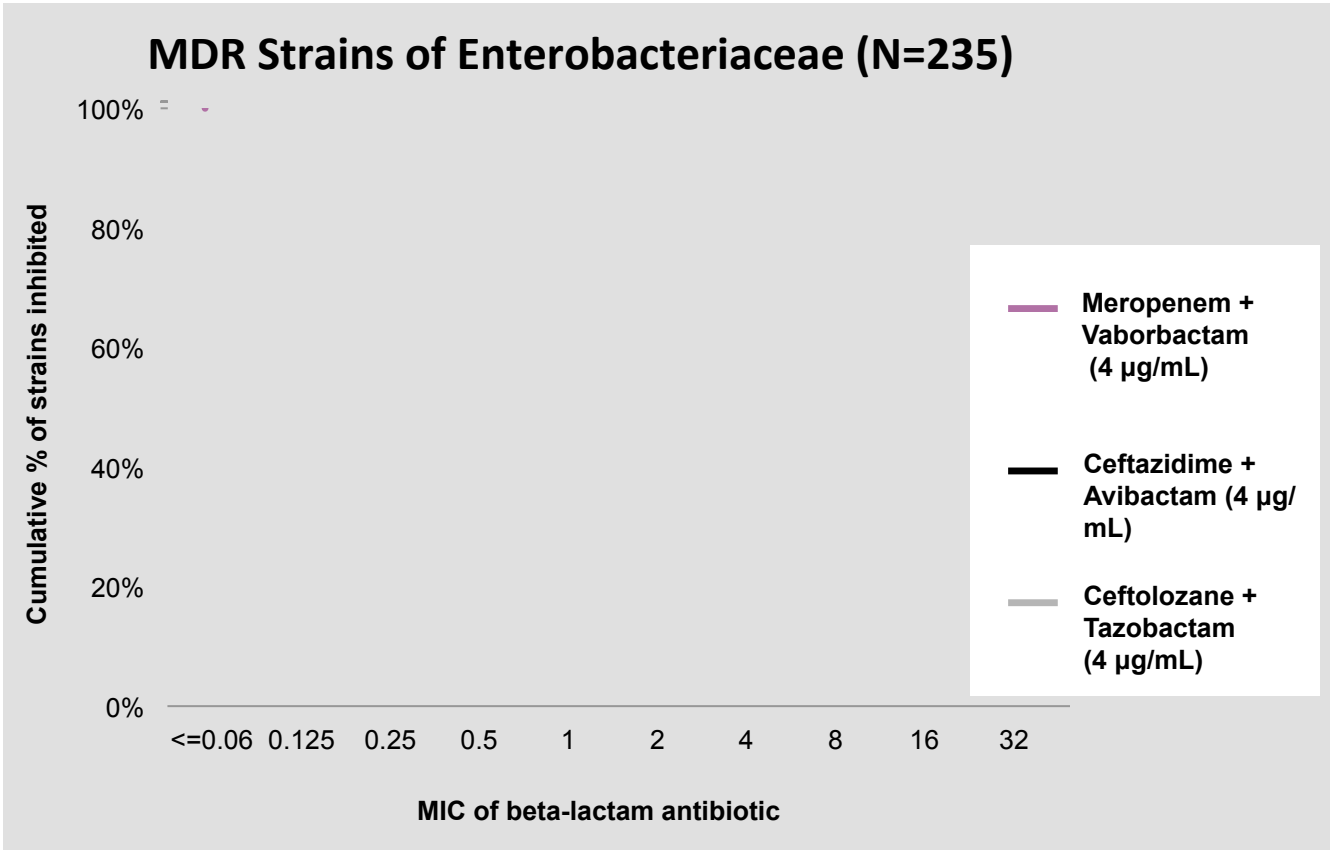
In Vitro Comparison of Meropenem-Vaborbactam vs. Recently Approved Cephalosporin-Based Beta-lactamase Inhibitor Combinations



N=235	MIC_{50}	MIC_{90}
Meropenem Alone	0.125	32
+ Vaborbactam (4 µg/mL)	**≤0.06**	**1**
Ceftazidime Alone	64	>64
+ Avibactam (4 µg/mL)	**0.5**	**4**
Ceftolozane	8	>32
+ Tazobactam (4 µg/mL)	**2**	**>32**

	Levofloxacin	Amikacin	Gentamicin	Tigecycline	Polymyxin B	Aztreonam	Cefepime	Ertapenem	Pip/Tazo
MIC_{90}	64	>32	>64	4	2	>128	32	32	>64

Data on file. The Medicines Company..

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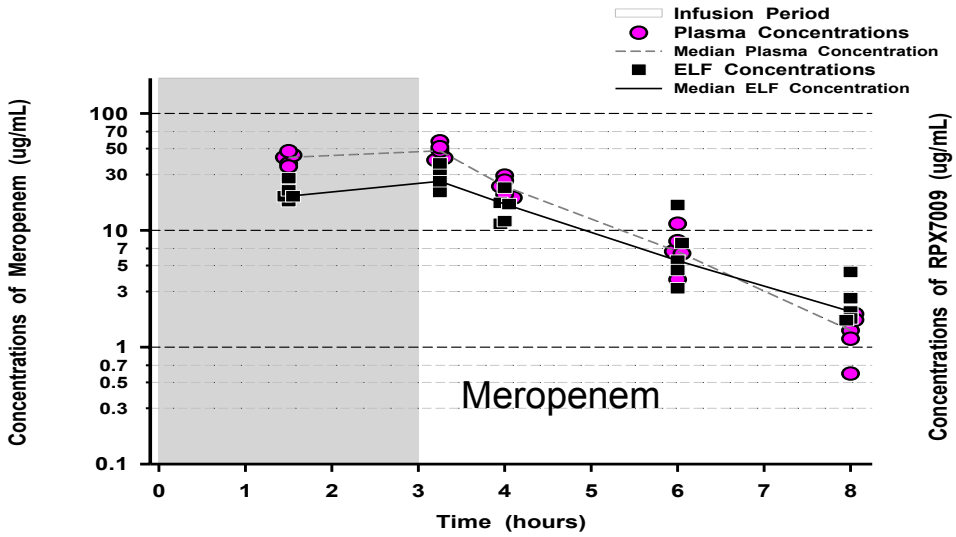
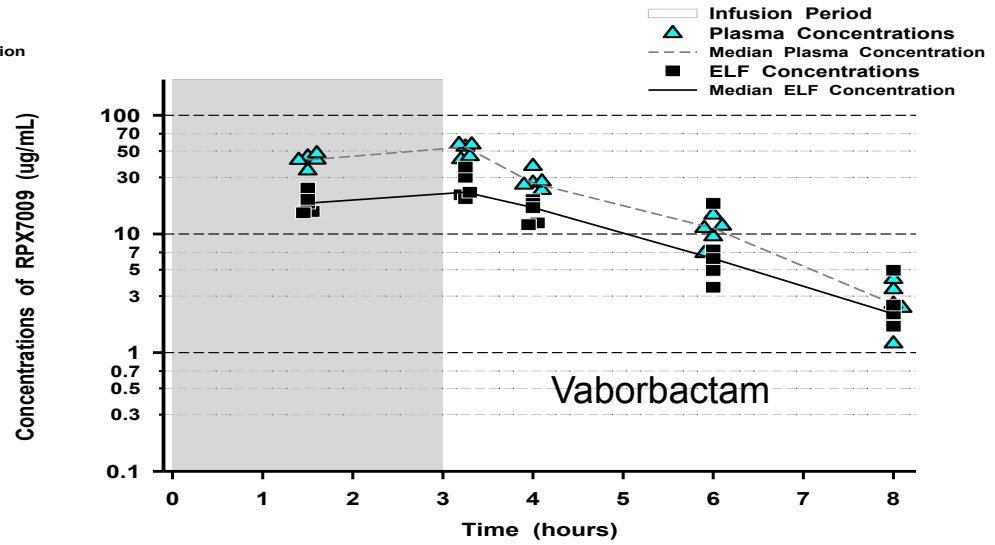
Matched PK in Plasma and ELF

Steady-State PK of Meropenem 2g / Vaborbactam 2g every 8 hrs as a 3hr infusion

(Wenzler et. al. AAC 2015;50;7232-9)



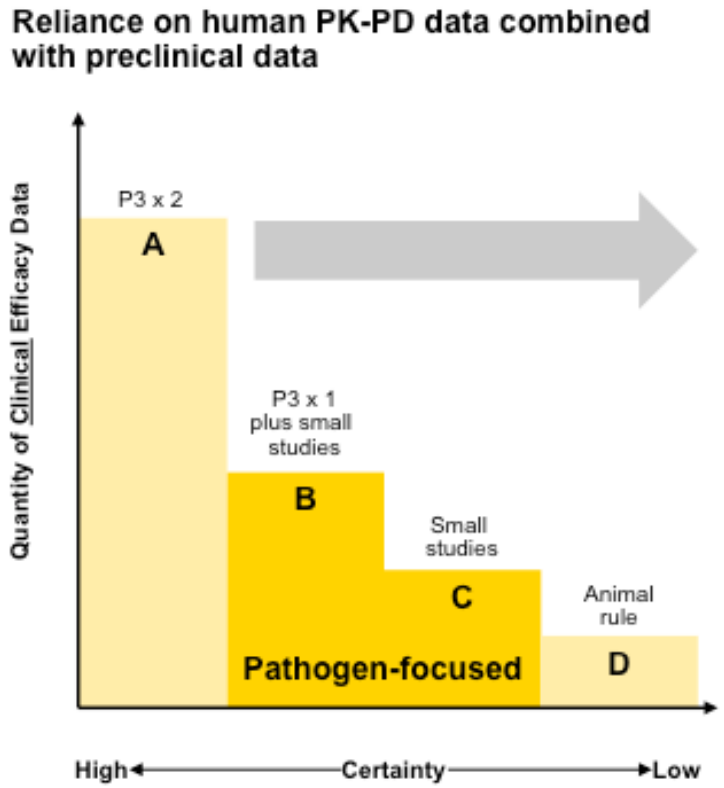


Meropenem AUC (ug-h/mL)	ELF	Plasma	E-P Ratio
Mean:	111.7	176.2	63%
Median:	102.4	176.8	58%

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

Why Study New Antimicrobials in Target Patient Populations With Pathogen(s) of Interest?

- PK-PD analyses important for translation of nonclinical data and data from larger trials
- Patients with MDR pathogens are usually not represented in usual guidance-directed pivotal studies
- Confirm appropriateness of dosage adjustments/exposures in special populations (e.g., renal impairment)
- Safety in target patient population
- Identify patient-specific effect modifiers *(see Bhavnani et. al. Tigecycline in HABP/VABP. AAC 2012;56:1065-72)*
- Inform clinicians in key patient population



Lancet Inf Dis 2013 Mar;13(3):269-75

VIEWPOINT

Antibiotic Development and Stewardship:

A Call for New Approaches

Brad Spellberg, MD
Los Angeles County + University of Southern California Medical Center, Los Angeles; and Division of Infectious Diseases, Department of Medicine, Keck School of Medicine at University of Southern California, Los Angeles.

Arjun Srinivasn, MD
US Centers for Disease Control and Prevention, Atlanta, Georgia.

Henry F. Chambers, MD
Division of Infectious Diseases, University of California at San Francisco.

JAMA 2/26/16

- Clinicians and stewardship professionals need data in the target patient population
  - "…for most drugs, appropriate use mirrors the way that **the drug was proven to be effective and safe in clinical trials**…"
  - "…the regulatory approval process and national practice guidelines should incorporate fundamental principles of antibiotic stewardship, in addition to safety and efficacy of the drug, **in defining approved indications and treatment recommendations**…"

("A novel idea: Study a drug designed for CRE in patients with CRE infection!")

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Meropenem-Vaborbactam Phase 3 Clinical Program

TANGO

Targeting Antibiotic Non-susceptible Gram-negative Organisms

	TANGO I	TANGO II
Features	*Site/Indication Focus* (Where CRE Frequently Found)	*Pathogen-Focus*
Patients	Complicated UTI and AP	cUTI/AP, cIAI, HABP, VABP and/or bacteremia known or suspected to be due to CRE
Design	Randomized 1:1 Double-blind	Randomized 2:1 Open-label
Comparator	Piperacillin-Tazobactam	"Best available therapy"
Total patients	550	~150
FDA/EMA guidance	Yes	Yes
BARDA contract	Yes	Yes
Status	*Completed; NI shown*	*Ongoing*

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TANGO II :
Prospective, Randomized Trial of Meropenem-Vaborbactam vs. "Best Available Therapy" in Patients with Suspected or Documented CRE Infection

TANGO
Targeting Antibiotic Non-susceptible Gram-negative Organisms

- Patients randomized in a 2:1 ratio to receive either (meropenem-vaborbactam) or BAT for 7-14 days total for treatment of serious infections due to known or suspected CRE.
  - CRE identified by either phenotypic or molecular testing within 72h prior to first dose of drug
  - Suspected CRE defined as CRE positive culture from any source within 90 days prior to D1.
- Clinical diagnosis of either: HABP/VABP, cUTI or AP, cIAI, or bacteremia not due to the other causes
- Open-label design with elements to reduce bias (blinded investigator, adjudication committee) in amended protocol.
- Pre-specified outcomes in each treatment group (e.g., percent overall cure (cure plus organism eradication) in patients with cUTI due to CRE treated with meropenem-vaborbactam vs. BAT)

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What is Best Available Therapy of CRE Infections?

- No results from prospective randomized trials in CRE infections with newly approved or old agents available
- Retrospective case series show reduced mortality, improved efficacy (especially bloodstream infections) with:
  - Carbapenem (meropenem)-based therapies
  - Combination therapy (variable)
    - Combo best with: meropenem-containing regimen vs. non-carbapenems; 2 "in vitro active" components;
  - Lower MICs….but what about PK or even info on dosage regimen???
- Risk factors for <u>poor</u> outcome:
  - Septic shock at presentation; high APACHE score
  - Inadequate initial antimicrobial therapy

Morrill et. al. OFID 2015
Tumbarello et. al. JAC 2015;70:2133-43
Tumbarello et. al. CID 2012;55:943-50
Tzouveleki et. al. Clin Micro Infect 2014;20:862-72
Daikos et. al. AAC 2014;58:2322-8
Qureshi et. al. AAC 2012;56:2108-13

Design and Planning a Clinical Trial of Meropenem-Vaborbactam in Patients with CRE Infections

Retrospective Study of Characteristics and Outcomes With "Best Available Therapy" in Patients with CRE Infection
(Alexander et. al., ICAAC 2015)

- **Objectives:**
  - Primary – Describe the treatment paradigms and outcomes associated with severe infections due to known or suspected CRE.
  - Secondary – Inform on the patient population, study inclusion/exclusion criteria, and **trial recruitment considerations** for a Phase 3 study of meropenem-vaborbactam in patients with infection due to known or suspected CRE.
  -
- **Study Design and Setting:**
  - Multi-center, retrospective study of patients with cUTI/AP, HABP, VABP and bacteremia due to confirmed CRE
  - 22 major medical centers in 4 countries: the U.S., Italy, Greece and the U.K.
  - Primary outcome: 28-day mortality
  - Secondary outcomes: Clinical cure rate, microbiological eradication rate, duration of hospitalization for index infection, duration of ICU stay.

TANGO
Targeting Antibiotic Non-susceptible Gram-negative Organisms

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Patients With CRE Have Co-Morbidities That Usually Result in Exclusion from Registration Trials

Baseline Characteristics of Patients

	cUTI (N=76)	HABP (N=21)	VABP (N=20)	Bacteremia (N=140)	All (n =257)
Duration of Hospitalization Prior to index CRE infection, days, mean (SD)[1]	13.3 (20.02)	22.7 (24.62)	17.5 (22.56)	27.5 (40.10)	**22.1 (33.45)**
Charlson Comorbidity Index, median (IQR)	3.0 (2.0-6.0)	4.0 (2.0-7.0)	3.0 (3.0-4.5)	3.0 (2.0-5.0)	**3.0 (2.0-5.0)**
Immunocompromised Condition, n (%)[2]	18 (23.7%)	7 (33.3%)	6 (30.0%)	36 (25.7%)	**67 (26.1%)**
Neutropenia, n (%)[3]	2 (2.6%)	0	1 (5.0%)	14 (10.0%)	**17 (6.6%)**
Prior Transplantation, n (%)[4]	10 (13.2%)	3 (14.3%)	4 (20.0%)	24 (17.1%)	**41 (16%)**
Chronic Renal Insufficiency, n (%)[5]	28 (36.8%)	5 (23.8%)	5 (25.0%)	47 (33.6%)	**85 (33.1%)**
Presentation with Septic Shock, n (%)[6]	15 (19.7%)	6 (28.6%)	8 (40.0%)	47 (33.6%)	**76 (29.6%)**
APACHE II mean (SD)[7]	23.5 (8.95)	18.6 (9.46)	21.4 (6.33)	22.1 (10.52)	**21.9 (9.74)**

[1]Refers to duration of hospitalization prior to index CRE infection

[2]Includes hematologic malignancy, prior bone marrow transplant, or received immunosuppressive therapy such as cancer chemotherapy, anti-rejection medications for transplantation, or long term (> 2 weeks) use of systemic steroids.

[3]Defined as an absolute neutrophil count < 500 cells/uL

[4]Defined as prior solid organ or bone marrow transplantation

[5]Defined as elevated blood urea nitrogen or creatinine levels compared to the site-specific reference range

[6]Defined as presentation with profound hypotension (SBP <90mmHg or a decrease in SBP of >40mmHg from baseline that was not responsive to fluid challenge) plus known infection.

[7]Acute Physiology and Chronic Health Evaluation II score at time of onset of CRE infection.

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Retrospective Study of Characteristics and Outcomes With "Best Available Therapy" in Patients with CRE Infection

(Alexander et. al., ICAAC 2015)

Outcomes of Serious Infections Due to Known CRE, According to Infection Type and Overall.

	Number (%) of Patients				
	Infection Type				
Outcome	**cUTI/AP (n= 76)**	**HABP (n= 21)**	**VABP (n = 20)**	**Bacteremia (n = 140)**	**All (n= 257)**
Duration of hospitalization for index CRE infection (mean ±SD)	8.1 (12.6)	11.7 (7.2)	12.4 (6.4)	17.9 (17.5)	14 (15.4)
Duration of ICU stay related to index CRE infection (mean ±SD)	3.6 (11.5)	7.7 (16.1)	14.1 (12.0)	9.5 (15.8)	8.0 (14.7)
Number (%) with clinical cure (PI-ascertained)	54 (71%)	9 (43%)	9 (45%)	74 (53%)	146 (57%)
Number (%) alive at Day 28*	51 (67%)	12 (57%)	12 (60%)	82 (59%)	157 (61%)
28 day mortality (%)*	**14 (18%)**	**7 (33%)**	**7 (35%)**	**45 (32%)**	**73 (28%)**

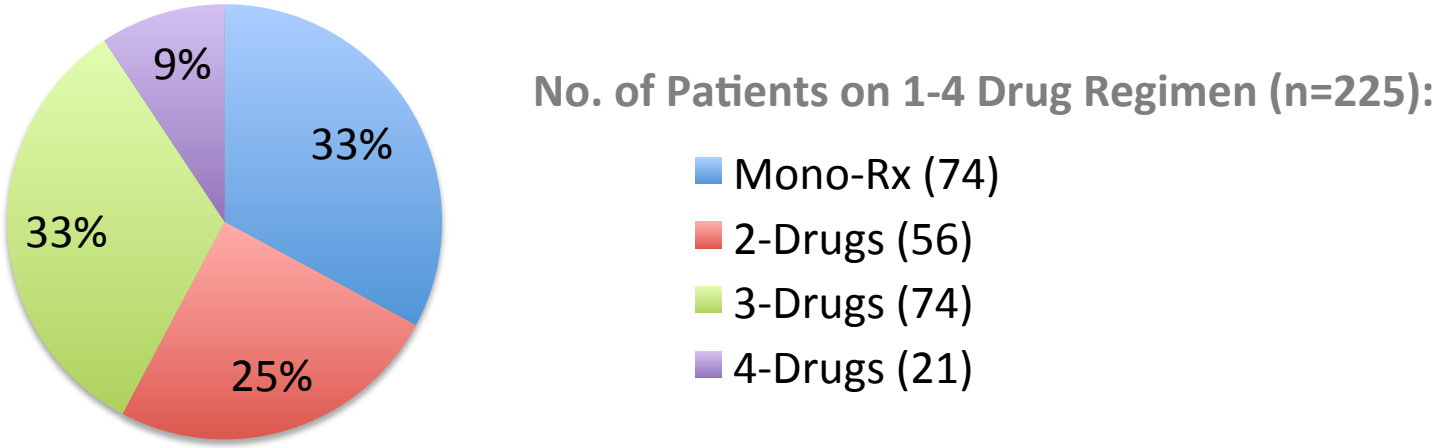
*Does not include patients for whom mortality status on Day 28 was missing (11 cUTI/AP, 2 HABP, 1 VABP, 13 bacteremia)

"Best-Available Therapy": Not Very Active, No Consensus!

(Alexander et. al., ICAAC 2015)

Drug	% Non-Susc In Vitro
Gentamicin	108/254 (42.5%)
Colistin/Polymyxin B	44/173 (25.4%)
Tigecycline	60/161 (37.3%)
Ciprofloxacin	178/203 (87.7%)

- **69 different directed-therapy antimicrobial regimens!**
- **No obvious clinical benefit of combo vs. mono-Rx**



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How the Results of the Retrospective Study Guided the Inclusion/Exclusion Criteria for TANGO II

- These results were used to modify the inclusion and exclusion criteria of an ongoing Phase 3 trial of a novel BL/BLI (TANGO II a.k.a. Study 506):
  - Protocol was amended to allow enrollment of patients with:
    - Immunocompromised: including prior transplantation, neutropenia, receipt of chemotherapy.
    - Renal disease: including patients on standard hemodialysis
    - Liver disease (except those meeting Hy's criterion)
    - Revised prior exclusion concerning multiple co-morbidities:
  - *Removed exclusion: "Evidence of immediately life-threatening disease, including, but not limited to, acute heart failure, shock, acute coronary syndrome, unstable arrhythmias, hypertensive emergency, acute hepatic failure, active gastrointestinal bleeding, profound metabolic abnormalities (e.g., diabetic ketoacidosis), or acute cerebrovascular events, OR in the opinion of the Investigator, the subject is unlikely to survive the duration of the treatment."*

Changed to: " Evidence of immediately life-threatening disease where in the opinion of the investigator, the subject is unlikely to survive more than 72 hours from randomization"

A Few Words…
Clinical Trial Networks and Labeling

- Clinical trial networks
  - We believe these are most useful in the setting of studying patients with resistant pathogens like CRE
  - Could help identify "BAT" regimens
    - Standardize access for use rapid diagnostic/susceptibility/resistance testing systems and strategies for use
    - Common control for evaluation of new agents and strategies
  - MDCO & Achaogen are battle worn: A network would preserve this experience
- Labeling
  - Need to communicate experience in patient populations and pathogens of interest
  - If a CFR needs to be changed, let's change it

Summary

- Don’t expect trials focusing on pathogens to yield same patients as a guidance-directed registration trial in indications
- Don’t do these trials for inferential testing
- Studies in target patient populations are important to bridge to nonclinical PK-PD studies and larger clinical trials
- These studies are difficult, but important and enroll-able; clinical trial networks would be most useful here
- Information needs to be included in product labeling

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