

Treatment strategies for carbapenem-resistant enterobacteriaceae: The past, the present, and the future

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Game plan!

- Set the stage: understand limitations of “historic” options for the treatment of invasive infections due to CRE
- Combination therapy vs monotherapy: Is it better?
- Where does ceftazidime/avibactam fit in?
- What is in the late stage pipeline for the management of CRE?

Traditional options for CRE:

Leaving a little something to be desired

Traditional options	Limitations
Beta-lactams	Borderline in vitro susceptibility, ? ability to optimize PK/PD, inoculum effect concerns, presence of enzymes to hydrolyze, co-production of other beta-lactamases
Polymyxins	Difficult (impossible) to safely and optimally administer, heteroresistance, optimal agent? Right dose?
Aminoglycosides	Questionable utility outside of UTIs as monotherapy
Tigecycline	Bacteriostatic, questionable activity in serum, lungs, urine; resistance development on therapy
Fosfomycin	Only (currently) available in US as 3 gram x 1 oral “sachet”

The case for combination therapy

- This is not the typical “double coverage” argument
- Monotherapy options stink!
 - Difficult (or impossible) to optimize
 - Resistance development on therapy common
- Synergy data impressive
 - Polymyxins
 - Aminoglycosides

Predictors of mortality in patients with bloodstream infections caused by KPC-producing *Klebsiella pneumoniae* and impact of appropriate antimicrobial treatment

Clin Microbiol Infect 2011; 17: 1798–1803

O. Zarkotou¹, S. Pournaras², P. Tselioti³, V. Dragoumanos⁴, V. Pitiriga⁵, K. Ranellou⁵, A. Prekates³, K. Themeli-Digalaki¹ and A. Tsakris⁵

- Retrospective analysis of 35 patients with KPC bloodstream infections
- Amongst patients who received at least 48 hours of appropriate treatment
 - Mortality was seen in 0/20 (0%) of patients receiving definitive combination therapy vs 7/15 (47%) with monotherapy ($p = 0.001$)
 - Most common combination was colistin + tigecycline ($n = 9$) but wide range of 2-3 drug combinations given
- Significance of combination therapy fell out of the multivariate model

Treatment Outcome of Bacteremia Due to KPC-Producing *Klebsiella pneumoniae*: Superiority of Combination Antimicrobial Regimens

Antimicrob. Agents Chemother. 2012, 56(4):2108. |

Zubair A. Qureshi,^a David L. Paterson,^{a,b} Brian A. Potoski,^{a,c} Mary C. Kilayko,^d Gabriel Sandovsky,^d Emilia Sordillo,^{d,e} Bruce Polsky,^{d,e} Jennifer M. Adams-Haduch,^a and Yohei Doi^a

- Retrospective analysis of 41 patients with KPC bloodstream infections
- Amongst patients who received definitive therapy against pathogen (n = 34)
 - Mortality was seen in 2/15 (13%) of patients receiving definitive combination therapy vs. 11/19 (57%) with monotherapy (p = 0.01)
 - Most common combination was polymyxin + carbapenem (n = 6) but wide range of 2-drug combinations given
- Combination definitive therapy remained significant in multivariate model (OR 0.07 (0.009 – 0.71)*
 - model included all patients, even those who didn't get active definitive therapy

Predictors of Mortality in Bloodstream Infections Caused by *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae*: Importance of Combination Therapy

Mario Tumbarello,¹ Pierluigi Viale,² Claudio Viscoli,³ Enrico Maria Trecarichi,¹ Fabio TumiETTO,² Anna Marchese,⁴ Teresa Spanu,⁵ Simone Ambretti,⁶ Francesca Ginocchio,³ Francesco Cristini,² Angela Raffaella Losito,¹ Sara Tedeschi,² Roberto Cauda,¹ and Matteo Bassetti^{3,7}

- Retrospective analysis of 125 patients with KPC bloodstream infections
- Mortality rates: 27/79 (34%) combination therapy vs. 25/46 (53%) monotherapy
 - Mortality advantage driven by 3-drug combination therapy with colistin + tigecycline + meropenem (4/23 (17%) died with this combination)
- In multivariate analysis colistin + tigecycline + meropenem protective against death (OR 0.11 (0.02 – 0.69))

Where it got a little more interesting....

Survival amongst patients receiving meropenem as part of combination regimen

Meropenem MIC (mg/L)	Total N	Non-survivors	Survivors
1	1	0	1 (100)
2	4	0	4 (100)
4	10	2 (20)	8 (80)
8	4	1 (25)	3 (75)
≥ 16	17	6 (35)	11 (65)
Total	36	9 (25)	27 (75)

Carbapenemase-Producing *Klebsiella pneumoniae* Bloodstream Infections: Lowering Mortality by Antibiotic Combination Schemes and the Role of Carbapenems

Antimicrobial Agents and Chemotherapy April 2014 Volume 58 Number 4 p. 2322–2328

George L. Daikos,^a Sophia Tsaousi,^b Leonidas S. Tzouvelekis,^c Ioannis Anyfantis,^a Mina Psychogiou,^a Athina Argyropoulou,^d Ioanna Stefanou,^e Vana Sypsa,^f Vivi Miriagou,^g Martha Nepka,^d Sarah Georgiadou,^a Antonis Markogiannakis,^h Dimitris Goukos,^a Athanasios Skoutelis^b

- Retrospective analysis of 205 patients with CRE bloodstream infections (175 had definitive therapy with at least 1 active agent)
- Mortality rates: 28/103 (27%) combination therapy vs. 32/72 (44%) monotherapy ($p = 0.018$)
- Mortality rates with 2-3 drug combinations as a function of having a carbapenem
 - Carbapenem sparing regimens 22/72 (31%)
 - Carbapenem containing regimens 6/31 (19%)
 - If carbapenem added to active agents and carbapenem MIC was >8 , mortality was 11/31 (36%)!!

Maybe it doesn't HAVE to be carbapenem-based...

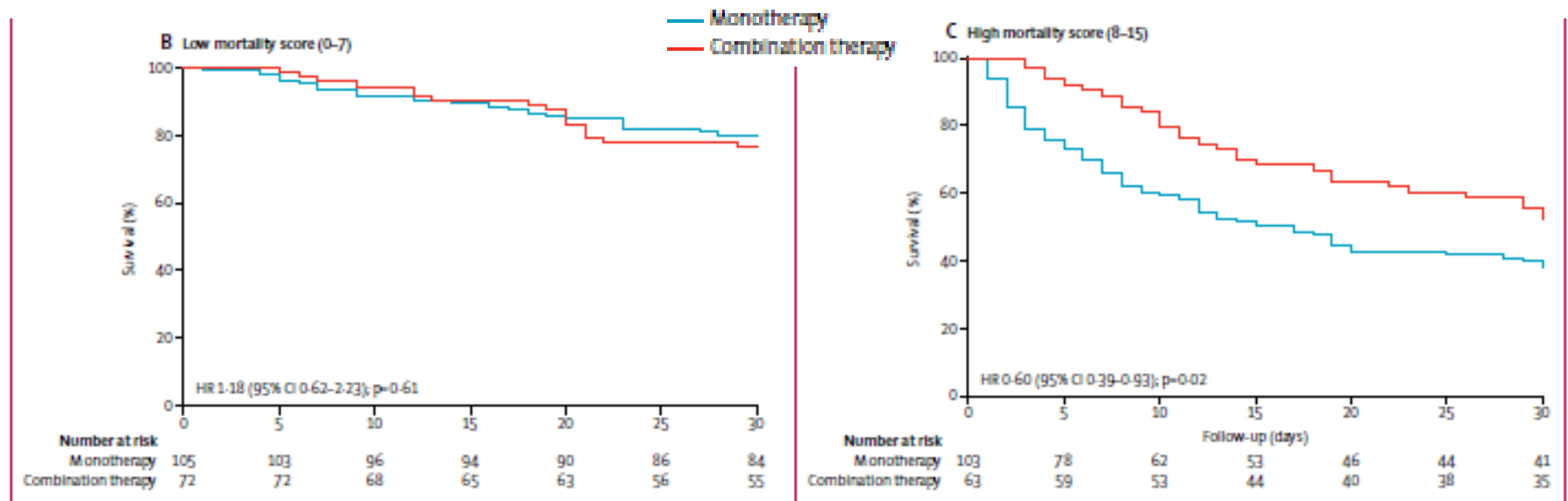
Carbapenem-Sparing Antibiotic Regimens for Infections Caused by *Klebsiella pneumoniae* Carbapenemase-Producing *K. pneumoniae* in Intensive Care Unit

Francesco Sbrana,¹ Paolo Malacarne,² Bruno Viaggi,² Sergio Costanzo,³ Piero Leonetti,³ Alessandro Leonildi,⁴ Beatrice Casini,⁵ Carlo Tascini,⁴ and Francesco Menichetti⁴

¹Fondazione Toscana Gabriele Monasterio, ²U.O. Anestesia e Rianimazione-Pronto Soccorso, Azienda Ospedaliera Universitaria Pisana, ³U.O. Medicina di Laboratorio e Diagnostica Molecolare, Azienda Ospedaliera Pisana, ⁴U.O. Malattie Infettive, Azienda Ospedaliera Universitaria Pisana, and ⁵Department of Translational Research, NTMS, University of Pisa, Pisa, Italy

- 26 patients with KPC infections
 - 16 VAP, 7 BSI, 2 UTI, 1 peritonitis
- Trauma ICU population
- Success 24/26 (92%)
- Various 2-3 drug regimens of tigecycline, colistin, gentamicin, and fosfomycin
- 1 tigecycline monotherapy

Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study

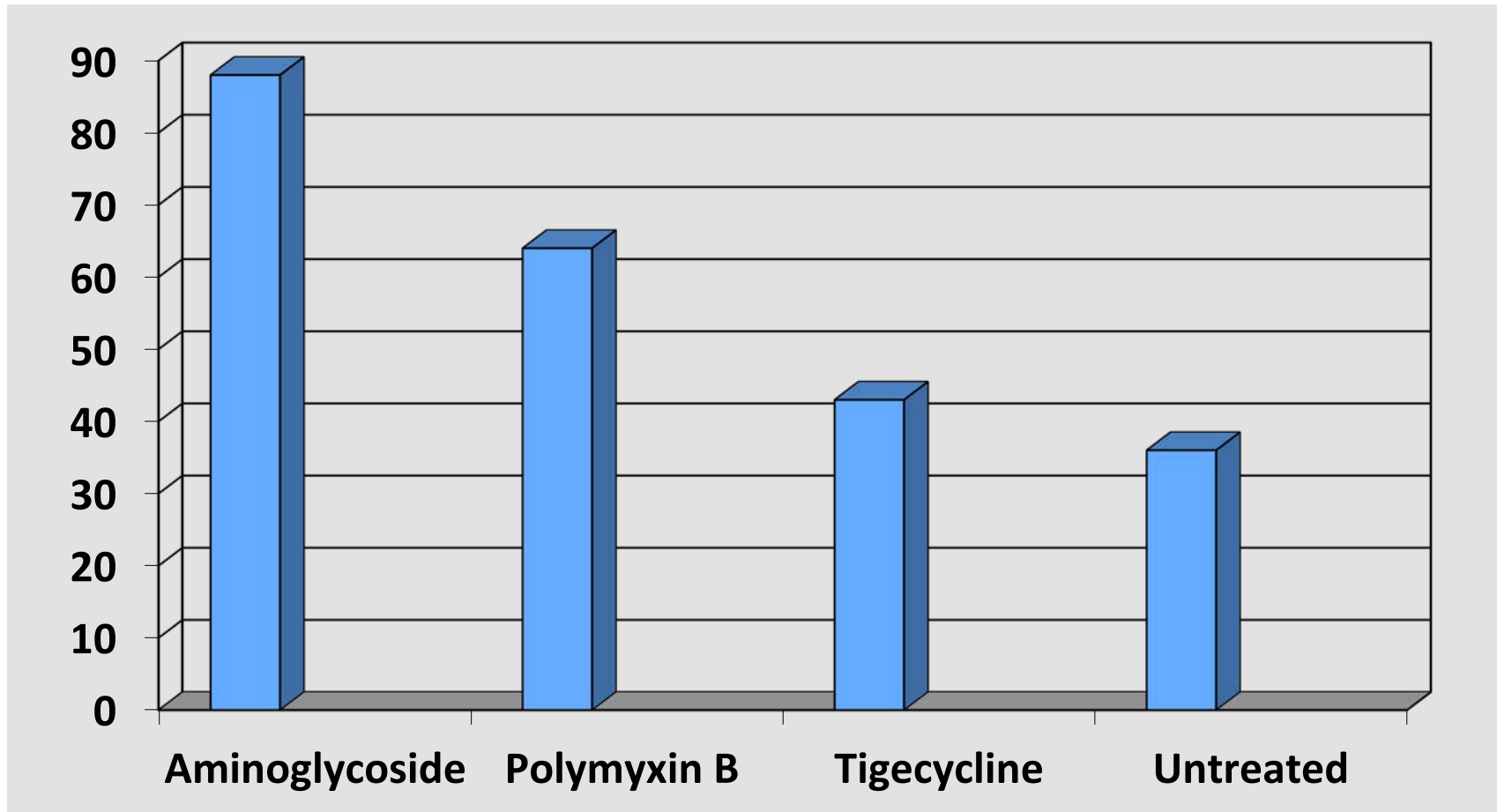


So what do these data tell us?

- It appears, that in patients with invasive CRE infections giving combination therapy with 2 (or more) ACTIVE agents decrease mortality
- Perhaps, it is only warranted in patients with higher severity of illness
- Which combination is optimal remains unclear
 - 2 or 3 agents?
 - Do I need a carbapenem? What if elevated MIC?
 - Do I need a polymyxin?

DISCLAIMER:

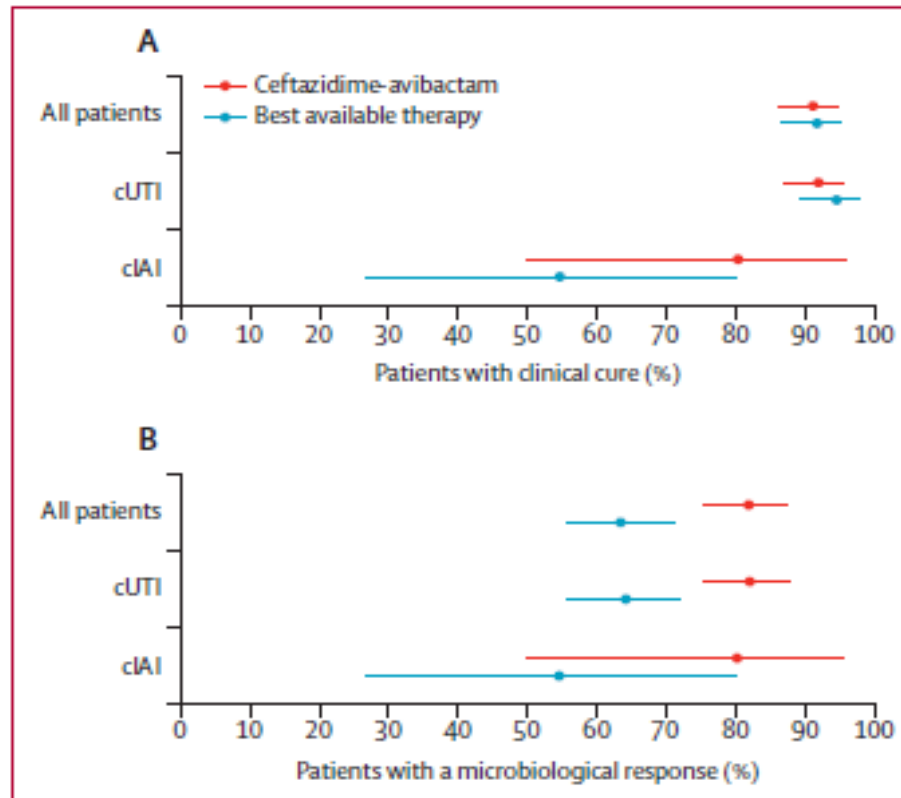
Not all infections are created equal



* Microbiological eradication rate in bacteruria

Ceftazidime/avibactam

Organism	Ceftazidime	Ceftazidime	CAZ/AVI	CAZ/AVI C90	Fold reduction
KPC producing K.pneumoniae				1	≥ 512
OXA-48 producing K.pneumoniae				.5	1024



Hot off the press!

Characteristics	C-A (n=13)	CB + AG (n=25)	CB + COL (n=30)	Other ¹ (n=41)	P-value
Primary bacteremia, n (%)	3 (23)	6 (24)	5 (17)	14 (34)	0.41
Secondary bacteremia, n (%)	10 (77)	19 (76)	25 (83)	27 (66)	0.41
• Abdominal	2	12	16	20	
• Respiratory	3	2	6	3	
• Urinary tract	5	2	2	4	
• Soft tissue	0	3	1	0	
2 or more active agents*, n (%)	5 (38)**	10 (40)***	9 (30)	8 (20)	0.28
Median time to active treatment (IQR)	55.7 (25 – 67)	52.5 (28 – 64)	67.9 (30 – 133)	65.0 (35 – 95)	0.23
Patient outcomes					
Clinical success, n (%)	11 (85)	12 (48)	12 (40)	15 (37)	0.02†
30-day survival, n (%)	12 (92)	17 (68)	21 (70)	28 (68)	0.37
90-day survival, n (%)	12 (92)	14 (56)	19 (63)	20 (49)	0.04‡
Persistent bacteremia, n (%)	0 (0)	1 (4)	5 (17)	8 (20)	0.13
Recurrent bacteremia, n (%)	2 (15)	5 (20)	3 (10)	9 (22)	0.60

Ceftazidime/avibactam: Monotherapy or in combination?

- Good question!



Clinical Outcomes, Drug Toxicity, and
Emergence of Ceftazidime-Avibactam
Resistance Among Patients Treated for
Carbapenem-Resistant
Enterobacteriaceae Infections

Ryan K. Shields,^{1,3,4,a} Brian A. Potoski,^{1,2,3,a} Ghady Haidar,¹ Binghua Hao,⁴ Yohei Doi,¹
Liang Chen,⁶ Ellen G. Press,¹ Barry N. Kreiswirth,⁶ Cornelius J. Clancy,^{1,4,5} and
M. Hong Nguyen^{1,3,4}

Aztreonam/avibactam- could be helpful for NDM



What does the pipeline have in store?

- Meropenem/Vaborbactam
- Imipenem/Relebactam
- Fosfomycin (IV formulation)
- Plazomicin
- Cefedirocol
- Eravacycline

The New inhibitors and the importance of the mechanism of CRE....

	Beta-lactamase inhibitor		
	Avibactam	Vaborbactam	Relebactam
Class A (KPC)	+	+	+
Class B MBLs (NDM, VIM, IMP)			
Class D (OXA-48)	+		

Meropenem/Vaborbactam

- Vaborbactam
 - Unique boronic acid beta lactamase inhibitor
 - Potent inhibition of KPC (more selective for KPC than other enzymes)

Species (n)	Meropenem		Meropenem-vaborbactam		Meropenem-vaborbactam	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>Klebsiella pneumoniae</i> (KPC+) (121)	8	64	0.06 / 4	2 / 4	0.03 / 8	0.5 / 8

MIC values in µg/mL

- All but 2 of these isolates (98.3%) were inhibited by 1 µg/mL meropenem combined with vaborbactam at 8 µg/mL

Meropenem/vaborbactam

Current status

- Phase III study for cUTI versus piperacillin/tazobactam (Tango 1)
 - Superior at early endpoint
 - Non-inferior at late endpoint
 - High dose meropenem the driver in outcomes
- Tango 2 study vs. Best Available Therapy (BAT) for CRE infections
 - Study ongoing
- Possibly available as soon as Q3 2017

Imipenem/relebactam

- Addition of an “avibactam” like beta lactamase inhibitor to imipenem

Species (n)	Imipenem		Imipenem - Relebactam	
	MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>bla_{KPC}-possessing K. pneumoniae</i> (111)	16	>16	0.25 / 4	1 / 4

MIC values in µg/mL

- Phase III studies ongoing
 - Versus colistin + imipenem for imipenem-resistant infections
 - Versus piperacillin/tazobactam for nosocomial pneumonia

Plazomicin

- Next-generation aminoglycoside (“neoglycoside”)
- In vitro activity against both Gram-positive and Gram-negative organisms
 - including isolates harboring any of clinically relevant aminoglycoside-modifying enzymes
 - But not those with ribosomal mutations
 - Much more potent than older aminoglycosides against CRE

Activity Against MDR Enterobacteriaceae from Greece

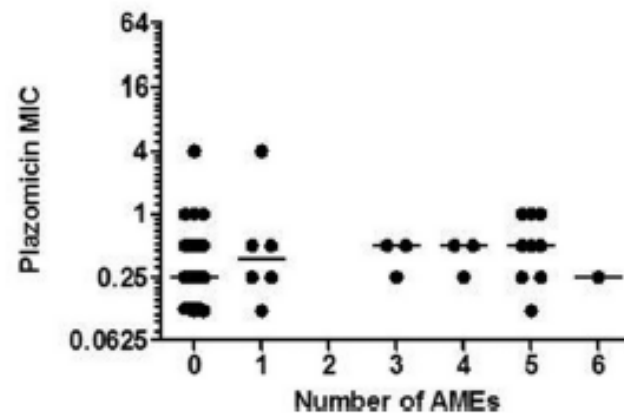
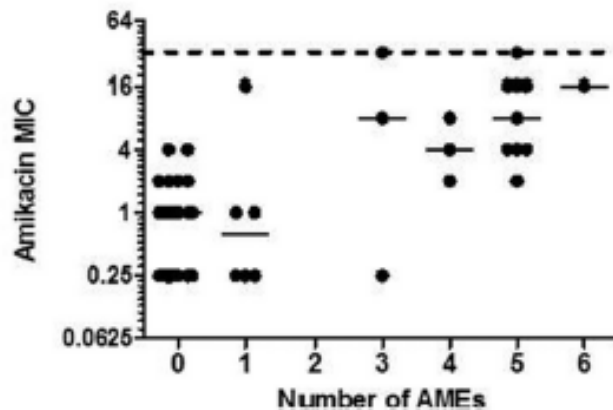
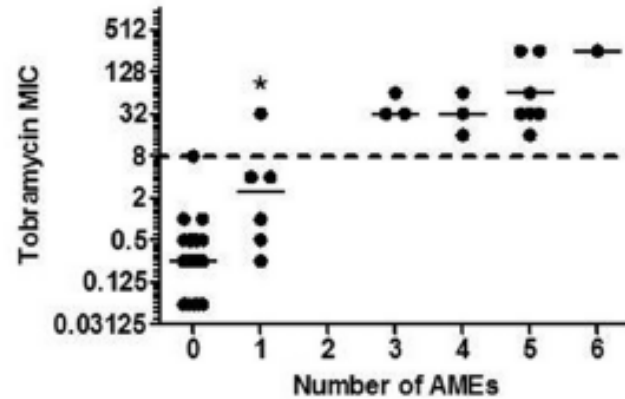
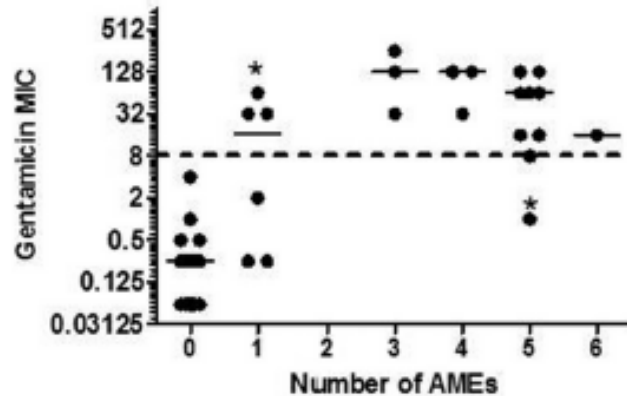
Table 2 Activities of plazomicin against 300 MDR enterobacterial isolates with different resistance phenotypes

Species	Phenotype	No. of isolates	MIC ($\mu\text{g/ml}$)						
			0.25	0.5	1	2	4	8	16
<i>Klebsiella pneumoniae</i>	KPC	25		7	12	5	1		
	ESBL, KPC	113		15	69	26	3		
	VIM	32		4	14	10	4		
	ESBL, VIM	43		8	22	9	4		
	KPC, VIM	10			7	3			
	ESBL, KPC, VIM	4			3	1			
	ESBL	14			9	4		1	
	Total	241		34	136	58	13		
<i>Escherichia coli</i>	KPC	9		3	4	2			
	VIM	5		2	3				
	ESBL, VIM	4	1		3				
	ESBL	15		3	8	4			
	Total	33	1	8	18	6			
<i>Enterobacter aerogenes</i>	KPC	1			1				
	ESBL, KPC	1		1					
	VIM	5			4	1			
	Total	7		1	5	1			
<i>Enterobacter cloacae</i>	KPC	2		1	1				
	VIM	15		8	6	1			
	KPC, VIM	1							
	ESBL, VIM	1			1				
	Total	19		10	8	1			

37%, 7%, 18% were susceptible to gentamicin, tobramycin, and amikacin, respectively

Why the enhanced activity?

Stability to aminoglycoside modifying enzymes

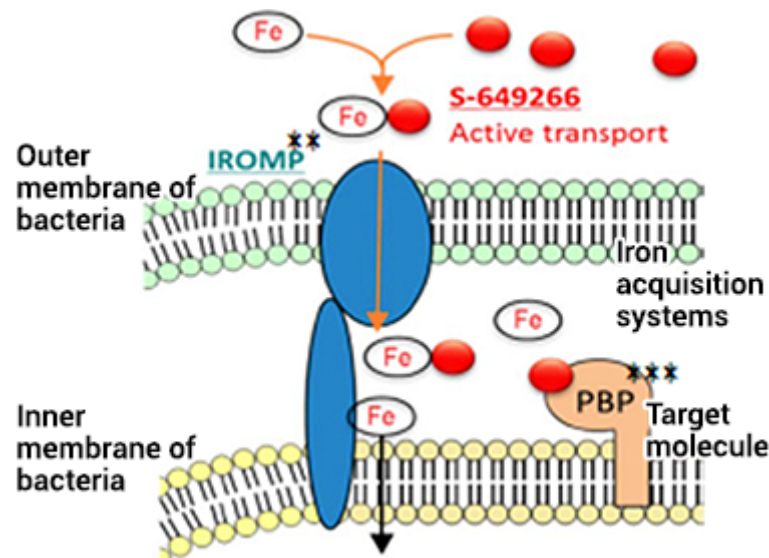


Plazomicin: Clinical trials

- A Phase 3, Multicenter, Randomized, Open-Label Study to Evaluate the Efficacy and Safety of Plazomicin Compared with Colistin in Patients with Infection Due to Carbapenem-Resistant Enterobacteriaceae (CRE) [CARE]
 - High level results presented at ECCMID: superiority (and less toxicity)
- Phase 3 study in UTI
 - Superiority seen over imipenem at late endpoint (and potentially a decrease in recurrent UTI)

Cefiderocol

- “Trojan horse” Siderophore cephalosporin
- Catechol group on cephalosporin chelates iron- uptake into cell via normal iron uptake channel
- Dissociates- and the structure is stable to clinically relevant beta-lactamases



Impressive activity!

Species/antibiotic	MIC (mg/L)			Resistance (%)		
	MIC range	MIC ₅₀	MIC ₉₀	S	I	R
<i>K. pneumoniae</i> (n=244)						
cefiderocol	≤0.03–4	0.5	1	NA	NA	NA
meropenem	2–>64	32	>64	0	3.3	96.7
ceftazidime	0.5–>64	>64	>64	1.6	1.6	96.7
cefepime	1–>16	>16	>16	0.4	1.2	98.3
ceftazidime/avibactam	0.12–>64	1	>64	NA	NA	NA
ceftolozane/tazobactam	1–>64	>64	>64	NA	NA	NA
aztreonam	≤0.5–>32	>32	>32	5.7	0.4	93.9
amikacin	≤4–>64	16	>64	61.5	14.8	23.8
ciprofloxacin	≤0.25–>4	>4	>4	4.9	0.8	94.3
colistin	≤0.5–>8	≤0.5	>8	62.7	0	37.3
tigecycline	≤0.25–4	0.5	2	90.2	7.4	2.5

- Current status
 - Completed Phase IIB/III study in cUTI – high level results reported at ECCMID- superior to imipenem

Eravacycline

- Synthetic fluorocycline that retains activity against common tetracycline-resistant organisms

110 CRE (largely KPC) from the USA

Table 3 MIC distributions of eravacycline and comparator agents against 110 CRE isolates

Antibiotic	MIC in $\mu\text{g ml}^{-1}$											
	≤ 0.5	1	2	4	8	> 8	16	> 16	32	> 32	64	> 64
Eravacycline	2	68	36	4								
Tetracycline			2 ^a	37	66				3			2
Tigecycline		4	97	9								

Global collection of 200 CRE

	<i>K. pneumoniae</i>			<i>E. coli</i>		
(MIC50/90)	NDM	VIM	OXA-48	NDM	VIM	OXA-48
Eravacycline	0.5/2	0.5/2	1/2	0.25/1	0.25/1	0.125/0.25
Tigecycline	4/8	4/8	4/4	2/8	2/4	1/2

Also has enhanced ELF and serum concentrations than tigecycline

Eravacycline Current Status

- Non-inferiority seen in Phase III trial for cIAI
- Failed to show non-inferiority in Phase III trial for cUTI
 - Problems related to using oral formulation at low dose (bioavailability ~10%)
- Recent guidance given from FDA
 - Second cIAI study needed for NDA
 - Just completed
 - New study to commence for once daily IV only therapy for cUTI
 - Revisiting the oral program

Summary

- Older therapeutic options come with significant limitations and combination therapy with these agents seems prudent
- Ceftazidime/avibactam offers promise and early results are encouraging- but more data are critically important to optimally utilize
- The pipeline could produce up to 4 agents for CRE by the end of the year in 2018, with a few others not far behind!
 - Strategies for optimal use will be crucial!

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