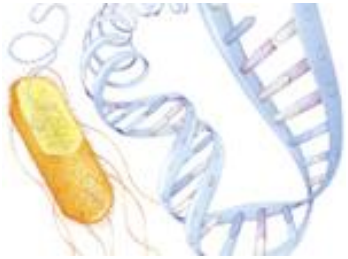

Carbapenemases and new antibiotics

Youri Glupczynski, MD, PhD

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De Ruwenberg – Den Bosch, 17th November 2017

Disclosure
Y. Glupczynski (CHU UCL Namur, Mont-Godinne)

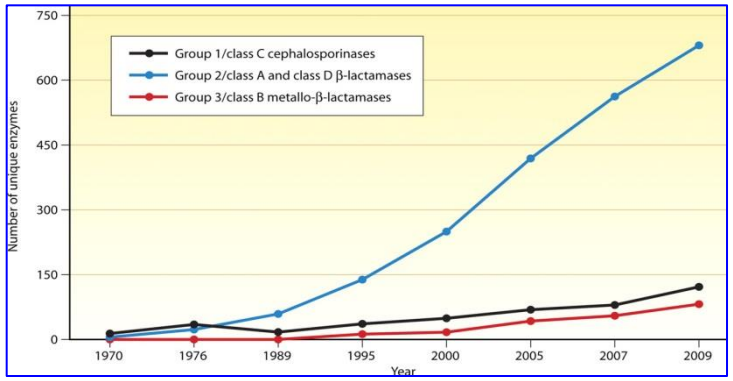
(potential) conflict of interest	None
For this meeting possibly relevant relationships with companies	None
• Sponsoring or research funding • Fee or other (financial) compensation • Shareholder • Other relationship, namely …	• • • •

Global problem of multidrug resistance: ESKAPE

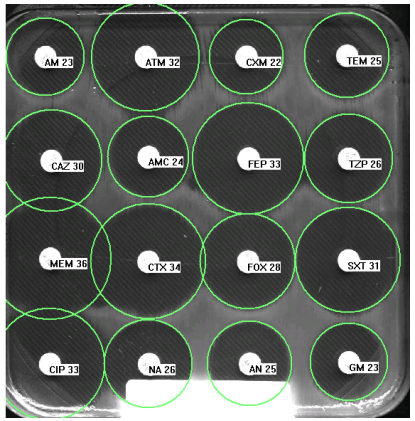
- ***E****nterococcus faecium:* VRE
- ***S****taphylococcus aureus:* MRSA, GISA
- ***K****lebsiella pneumoniae:* ESBL, CPE (VIM, KPC, OXA-48..)
- ***A****cinetobacter baumannii:* Carba -R (OXA..), (MDR, PDR, XDR)
- ***P****seudomonas aeruginosa:* Carba -R, (MDR, PDR, XDR)
- ***E****nterobacteriaceae:* ESBL, CPE (NDM, OXA-48..)

- In all healthcare sectors, travel importation and local spread
- Large diffusion of resistance (successful clones, horizontal transfer of mobile genetic elements

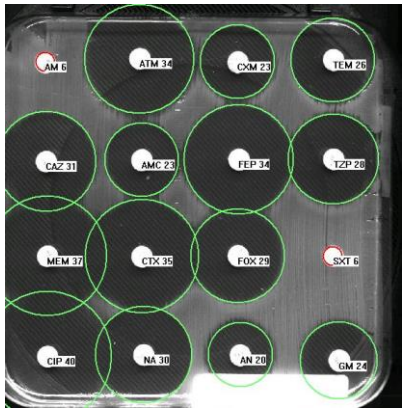
Evolving resistance in Enterobacteriaceae



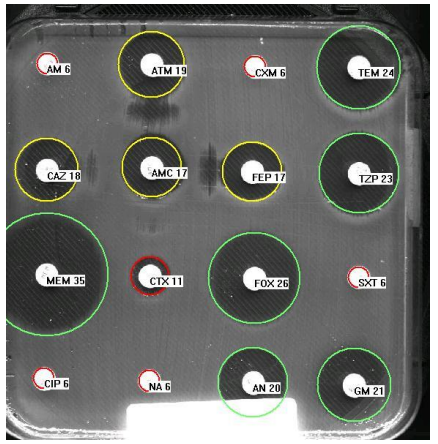
Wild-type



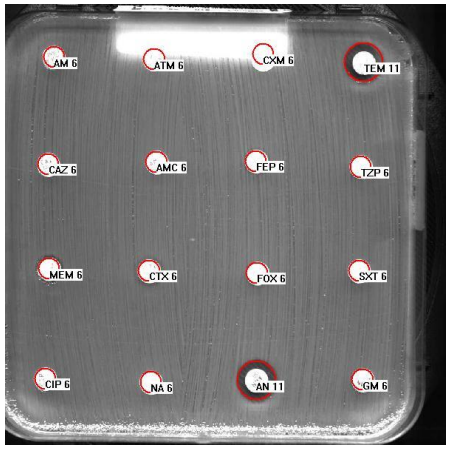
Penicillinases (TEM-1, SHV-1)



ESBLs (**CTX-M** >>SHV,TEM)



Carbapenemases

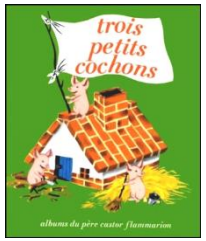


Pen R | Ceph R = MDR | Carb R = XDR!

1940

1970

1990



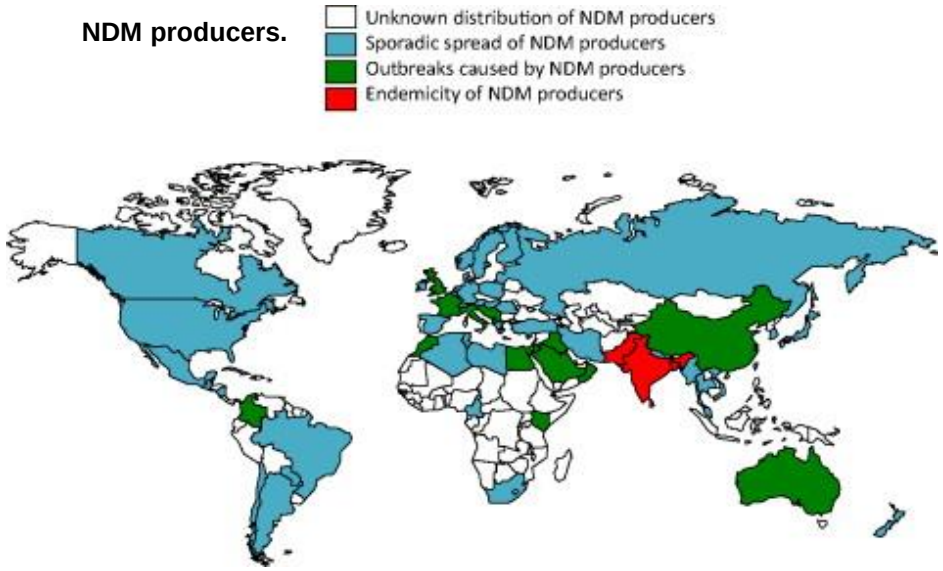
2000

* **MDR**: Multidrug resistance

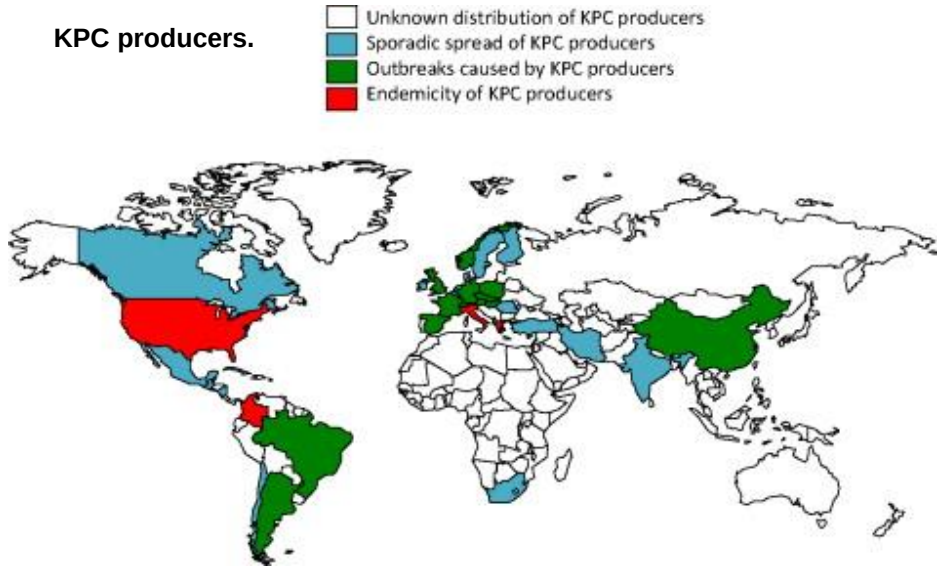
* **XDR**: Extensive drug resistance

Guidebook for CPE: A global issue

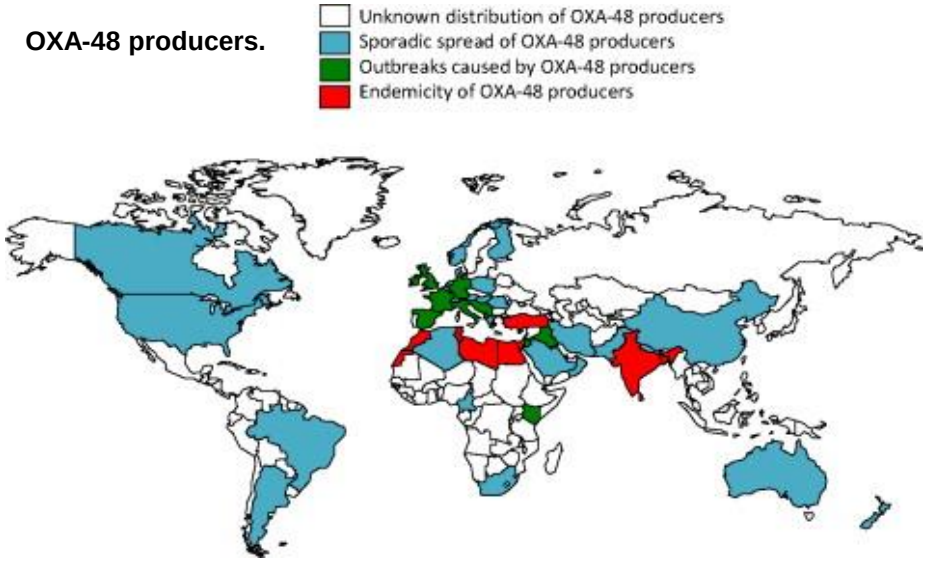
NDM producers.



KPC producers.



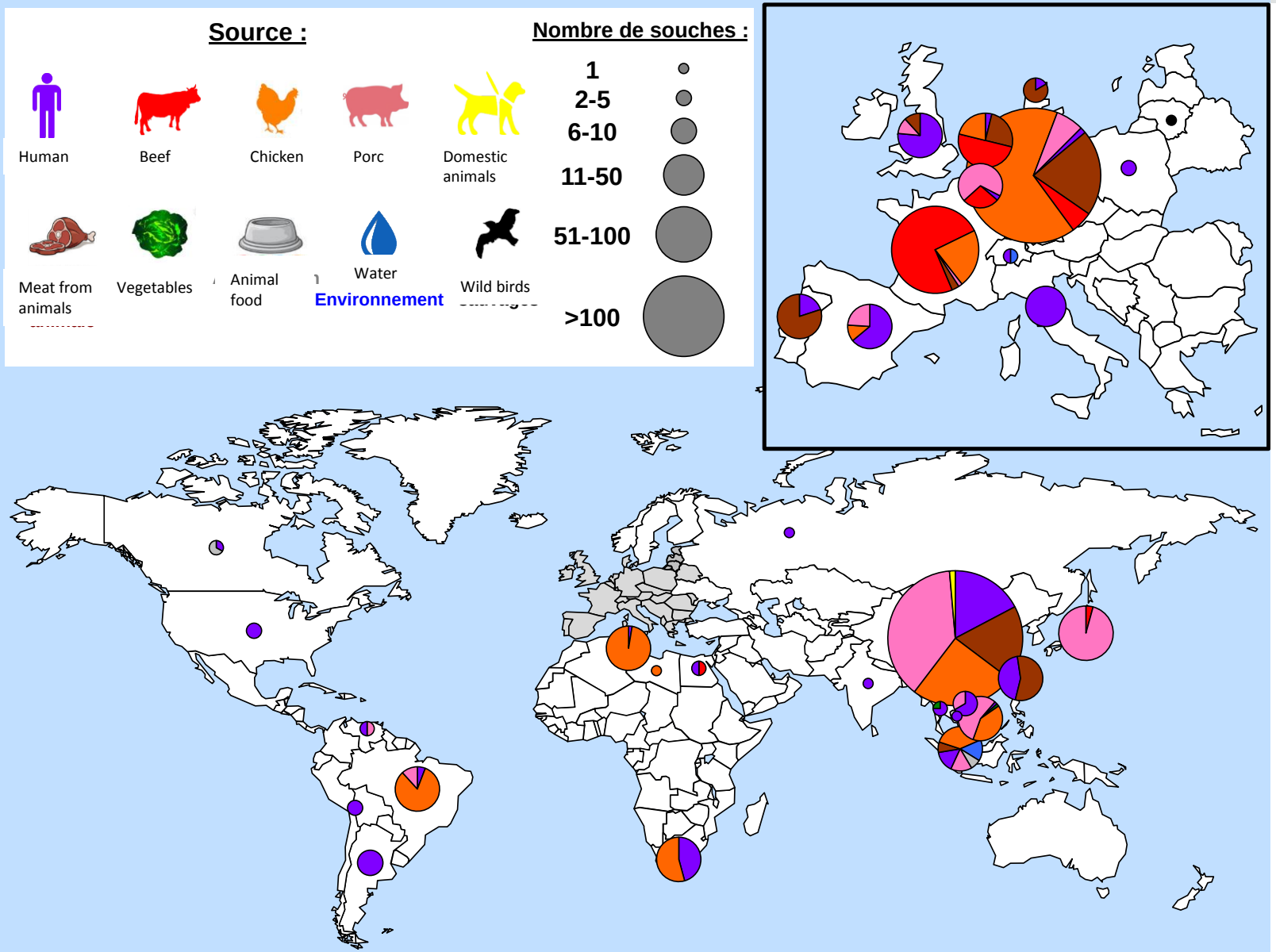
OXA-48 producers.



=> increased consumption of colistin

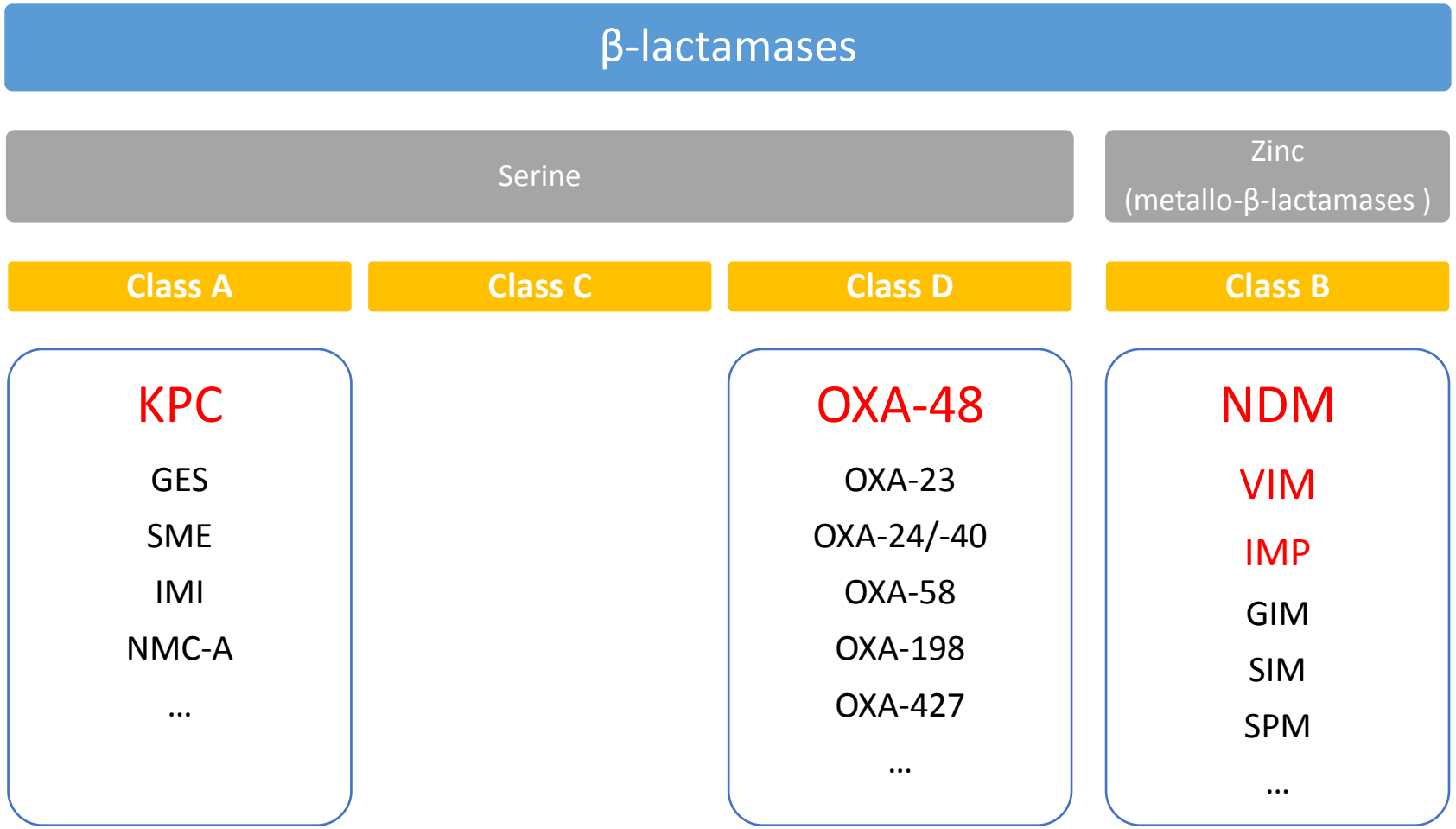
P. Nordmann, L. Poirel
CMI, 2014, 20, 821–830

Geographical distribution of mcr-plasmid mediated colistin resistant Enterobacteriaceae (August 2016)



Pfizer HEALT

Ambler classification of carbapenemases

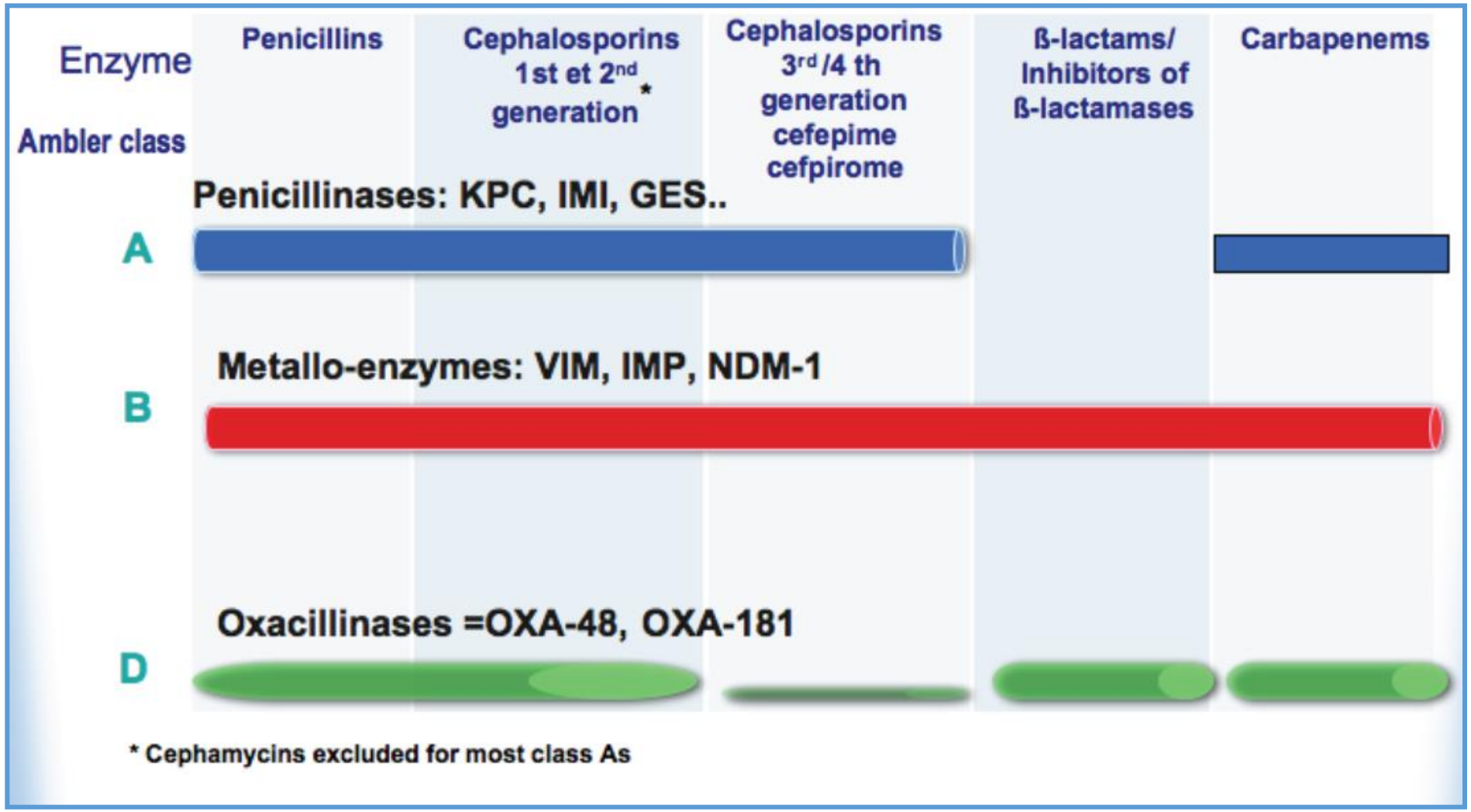


Large number of carbapenemases of different classes (some associations organisms-enzymes)

Resistance to most β-lactams

→ Major carbapenemases in Enterobacteriaceae

Classification of the different carbapenemases in *Enterobacteriaceae*



With courtesy from P. Nordmann

In vitro susceptibility rates (%) by disk diffusion (CLSI) of *Enterobacteriaceae* isolates in 2016 (n=824)

%S_DD_CLSI	OXA-48	KPC	NDM	VIM	NDM + OXA-48	KPC + VIM	non-CPE
Total n	282	33	65	55	6	2	373
Temocillin (Fuchs 1985)	0%	9%	3%	2%	0%	0%	38%
Piperacillin+tazobactam	1%	0%	0%	2%	0%	0%	29%
Cefotaxime	25%	0%	0%	2%	0%	0%	13%
Ceftazidime	41%	0%	0%	7%	0%	0%	18%
Cefepime	38%	0%	0%	15%	0%	0%	33%
Aztreonam	44%	0%	11%	58%	0%	0%	25%
Ertapenem	9%	3%	0%	24%	0%	0%	53%
Meropenem	46%	0%	0%	16%	17%	0%	70%
Gentamicin	52%	52%	38%	67%	33%	0%	68%
Amikacin	90%	30%	29%	87%	0%	100%	88%
Ciprofloxacin	30%	3%	25%	51%	0%	0%	30%
Cotrimoxazole	28%	6%	28%	16%	0%	0%	32%

TD HUANG et al., ECCMID 2017 'Poster P2017)
Data from the Belgian NRC (May 2017)

In vitro susceptibility rates (%) by micro broth dilution (CLSI) of CPE isolates in 2016 (n=111)

By carbapenemase type

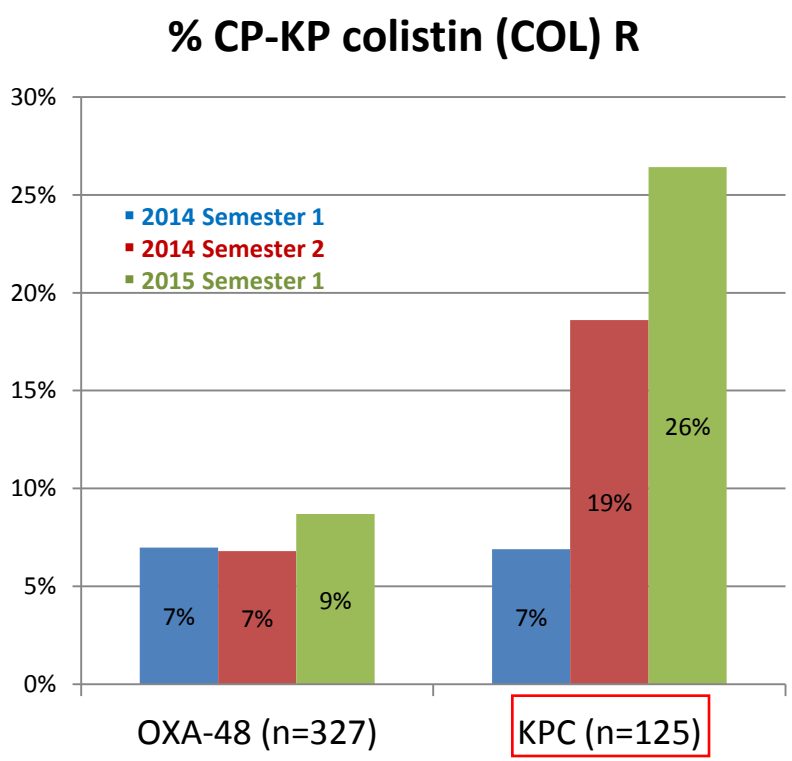
%S_MIC_EUCAST	Total	OXA-48	KPC	NDM	VIM	NDM + OXA-48	KPC + VIM
Total n CPE	111	68	8	14	10	2	1
Ceftolozane+tazobactam	17%	21%	0%	0%	0%	0%	0%
Meropenem	52%	75%	0%	0%	20%	0%	0%
Fosfomycin	75%	76%	38%	79%	80%	0%	0%
Tigecycline	78%	79%	100%	86%	60%	100%	0%
Colistin	82%	90%	88%	93%	100%	100%	100%

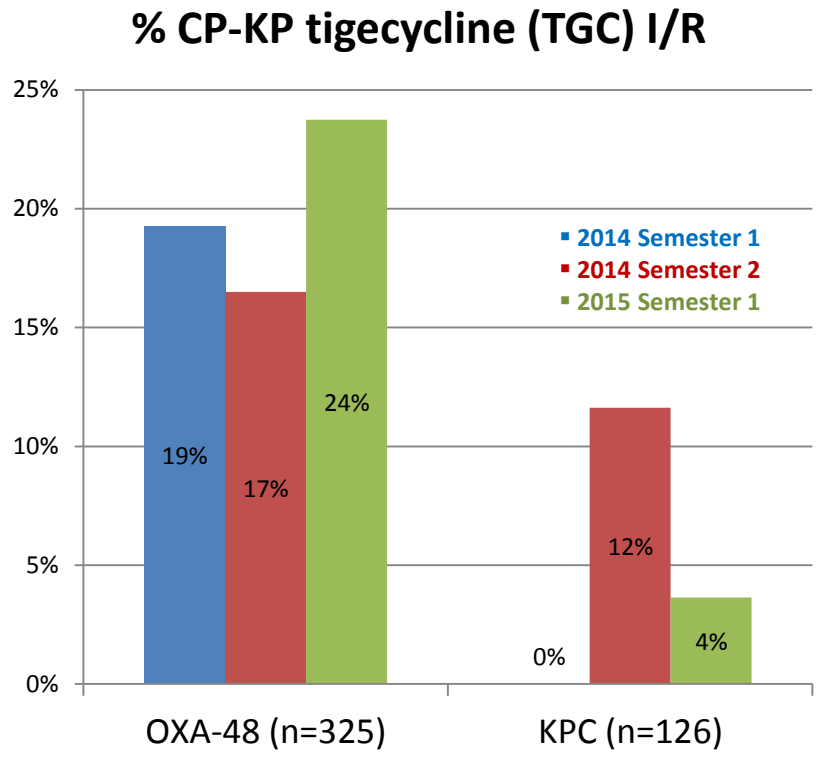
By species type

%S_MIC_EUCAST	Total	K. pneumoniae	E. coli	E. cloacae	C. freundii	K. oxytoca	Other species*
Total n CPE	111	61	17	15	7	2	9
Ceftolozane+tazobactam	17%	3%	59%	13%	0%	0%	67%
Meropenem	52%	55%	65%	27%	57%	0%	67%
Fosfomycin	75%	66%	100%	86%	100%	50%	67%
Tigecycline	78%	85%	100%	40%	86%	50%	56%
Colistin	82%	80%	100%	93%	100%	100%	11%

TD HUANG et al., ECCMID 2017 ‘Poster P2017)
Data from the Belgian NRC (May 2017)

Colistin and tigecycline R in CP-*K. pneumoniae* (CP-KP)





- **COL-R rate higher in KPC KP** (19%) vs OXA-48 KP (8%); p<0.001
- **TGC-I/R rate higher in OXA-48 KP** (20%) vs KPC KP (6%); p<0.001
- Global **increase of I/R rates in KP** from 2014 to 2015 for:
  - TGC-I/R (17% to 21%; p NS)
  - **COL-R** (6% to 14%; p=0.007) especially in **KPC KP** (p<0.001)

Huang et al. RICAI 2015. O113

- 2 *E. coli* OXA-48 isolates also COL-R and mcr-1 positive referred at NRC (1 in 2014, 1 in 2015)

WHO priority pathogens list for R&D of new antibiotics

- GAIN act USA (government)

(Generating Antibiotic

Incentive Now)

Innovative Medicine (public/private)

Initiative IMI) – EU

« New Drugs for Bad Bugs » (ND4BB)

Objective:
10 new drugs by 2020

Priority 1: CRITICAL#

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

Campylobacter, fluoroquinolone-resistant

Salmonella spp., fluoroquinolone-resistant

Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

Streptococcus pneumoniae, penicillin-non-susceptible

Haemophilus influenzae, ampicillin-resistant

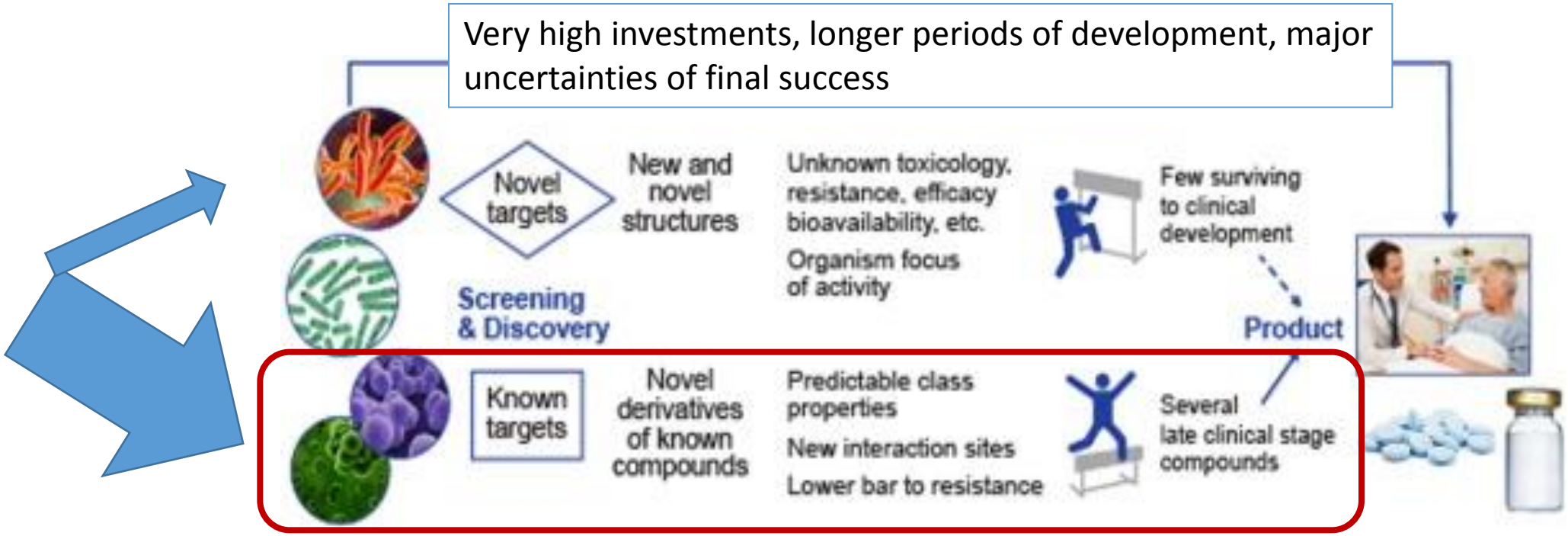
Shigella spp., fluoroquinolone-resistant

Mycobacteria (including *Mycobacterium tuberculosis*, the cause of human tuberculosis), was not subjected to review for inclusion in this prioritization exercise as it is already a globally established

World Health Organization

http://www.who.int/mediacentre/news/releases/2017/bacteria-antibiotics-needed/en/ (25/2/2017)

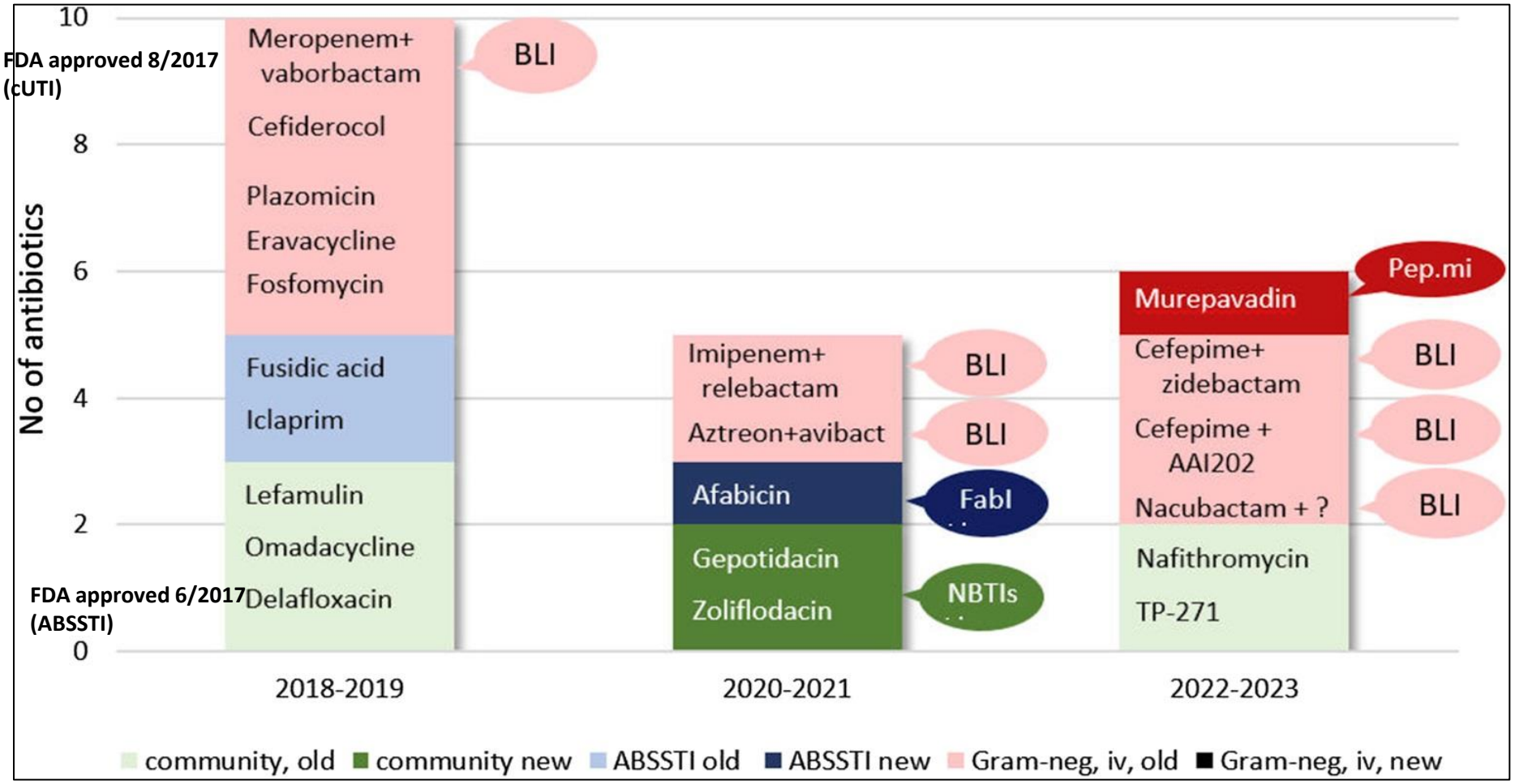
Antibiotics from Bench to Bedside



Applies to most of the 30 new drugs in late stage of clinical development

Fernandes P., Martens E., Biochem. Pharmacol. 2017
Wright H, Bonomo RA, Paterson, D CMI 2017: 23; 704-12

Potential US FDA approval of selected “new” antibiotics



U. Theureutzbacher, CMI 2017 23, 713-717DOI: (10.1016/j.cmi.2017.06.020)

Nr	Name	Class	FDA approved	IV	PO	Phase 3 completed	Phase 3 ongoing	various
1	Mero + Vaborbactam	Carbapenem + beta lactamase inhibitor (BLI)	+ (8/2017)	+	-	cUTI CRE infections		
2	Imi + Relebactam	Carbapenem + BLI	-	+	-	-	HAP/VAP CRE infections	
3	Cefiderocol	Siderophore Cephalosporin	-	+	-	cUTI	CRE infection NP	
4	Plazomicin	Aminoglycoside	-	+	-	cUTI CRE infections		
5	Eravacycline	Tetracycline	-	+	+ (?)	cIAI	cUTI	NDA submission not passed (oral form back to phase 2)
6	Fosfomycine IV	Epoxide	-	+	NA	cUTI		
7	Iclaprim	Inhibitor of dihydrofolate reductase	-	+	?	aBSSSI	aBSSSI	Activity against gram + (MSSA/MRSA, GAS) FDA approved for resp infection du to MRSA in CF patients
8	Lefamulin	Pleuromutiline	-	+	+	CAP		Gram +, Community resp pathogens + atypicals
9	Delafloxacin	FQ	+ (6/2017)	+	+	aBSSSI	CAP	cUTI planned
10	Omadacycline	Tetracycline	-	+	+	aBSSSI CAP		

Recent trials in complicated urinary tract infections and outcomes (Phase III, Non-inferiority)

Study	Design	Drug	Comparator	Duration of therapy	End point	Time end point assessed	Outcome drug versus Comparator
EPIC cUTI	Phase III Non-Inferiority	Plazomicin 15 mg/kg q24h	Meropenem 1 g q8h	4–7 days IV, option to change to PO levofloxacin to complete 7–10 days total treatment	Composite end point clinical cure and microbiological eradication mMITT TOC (FDA) Microbiological eradication TOC (EMA)	15–19 days after first dose	81.7% vs 70.1% 87.4% vs 72.1%
APEKs cUTI	Phase III Non-Inferiority	Cefiderocol 2g q8h	Imipenem-cilastatin 1 g/1 g q8h	7–14 days IV Mean duration 9 days	Composite end point clinical response and microbiological eradication mMITT TOC (FDA)	7 days after end of treatment	72.6% vs 54.6%
TANGO – 1	Phase III Non-Inferiority	Meropenem-vaborbactam 2 g/2 g q8h	Piperacillin-tazobactam 4.5 g q8h	5–10 days IV, option to change to PO levofloxacin after 5 days to complete 10 days total treatment	Clinical cure or improvement and microbiological eradication (FDA) Microbiological eradication mMITT TOC (EMA)	End of IV therapy (5 –14 days post first dose) 5–9 days post end of treatment	98.4% vs 94% 66.7% vs 57.7%
RECAPTURE	Phase III Non-Inferiority	Ceftazidime-avibactam 2.5 g q8h	Doripenem 500 mg q8h	10–14 days, option to change to PO antibiotics after 5 days	Composite end point clinical cure and microbiological eradication mMITT TOC (FDA) Microbiological eradication TOC (EMA)	21–25 days after randomization	71.2% vs 64.5% 77.4% vs 71%
ASPECT-cUTI	Phase III Non-Inferiority	Ceftolozane-tazobactam 1.5 g q8h	Levofloxacin 750 mg q24h	7 days	Composite end-point clinical cure and microbiological eradication mMITT TOC	5–9 days after end of treatment	76.9% vs 68.4%

Abbreviations: EMA, European Medicines Agency; FDA, US Food and Drug Administration;IV, intravenous; mMITT, microbiologically modified intention to treat; q24h, 24-hourly; TOC, test of cure.

Low/mild severity of infections/comorbidities
Hospitalized patients (Mixed of CA an HA, very few MDR (CRE)

H Wright et al., Clin Microbiol Infect 2017; 23: 704-712

Recent trials in complicated intra-abdominal infections and outcomes (Phase II/III, Non-inferiority)

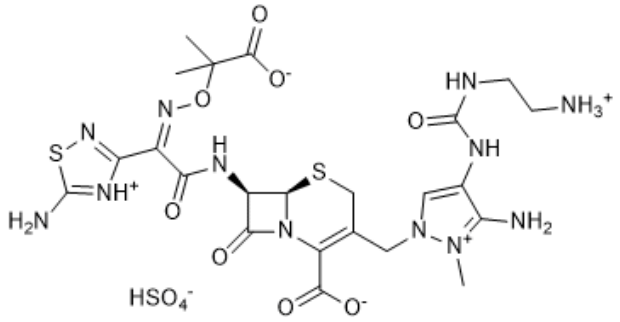
Study	Design	Drug	Comparator	Duration of therapy	Endpoint	Time end point assessed	Outcome drug versus Comparator
RECLAIM	Phase III Non-Inferiority	Ceftazidime-avibactam 2.5 g q8h and metronidazole 500 mg q8h	Meropenem 1 g q8h	5–14 days	Clinical cure mMITT TOC (FDA) Clinical cure in MITT and clinically evaluable (CE) population (EMA)	28–35 days post randomization	81.6% vs 85.1% 82.5% vs 84.9% (MITT) 91.7% vs 92.5% (CE)
ASPECT-cIAI	Phase III Non-Inferiority	Ceftolozane-tazobactam 1.5 g q8h and metronidazole 500 mg q8h	Meropenem 1 g q8h	4–14 days	Clinical cure MITT TOC	24–32 days post first dose study drug	83% vs 87.3%
IGNITE 1	Phase III Non-Inferiority	Eravacycline 1 mg/kg q12h	Ertapenem 1 g q24h	4–14 days	Clinical cure MITT TOC	25–31 days post first dose study drug	87% vs 88.8%
MK-7655-004	Phase II Assigned 1:1:1	Imipenem-cilastatin-relebactam 500 mg + 250 mg or 125 mg relebactam q6h	Imipenem-cilastatin	4–14 days	Favourable clinical response in microbiologically evaluable population	End of IV therapy	96.3% (relebactam 250mg) vs 98.8% (relebactam 125mg) vs 95.2%

Abbreviations: EMA, European Medicines Agency; FDA, US Food and Drug Administration; MITT, microbiological intention to treat; mMITT, microbiologically modified intention to treat; TOC, test of cure.

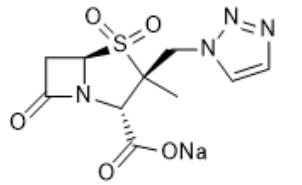
Ceftolozane/ tazobactam (« New/Old »)

- Novel expanded spectrum cephalosporin (C3-C4)
- Fixed combination with tazobactam (1 g/0.5 g IV Q8h)
- Activity preserved against the principal resistance mechanisms of ***P. aeruginosa***
  - Impermeability (OprD, deficiency/mutation)
  - Efflux pumps
  - AmpC overproducers
- **<u>Activity on ESBL and AmpC- producing *Enterobacteriaceae*</u>**
- **<u>Not active against CRE</u>** (KPC, MBLs, OXA-48)
- Limited activity against Staphylococci
- 1000/500 ou 2000/1000 mg/8h
- Urinary excretion: 92%
- Excellent diffusion in lung (alveolar fluids)

Ceftozolane-tazobactam (Zerbaxa®)



Ceftolozane sulfate
(CXA-101, FR264205



Tazobactam sodium salt

Approved by FDA 19 dec 2014

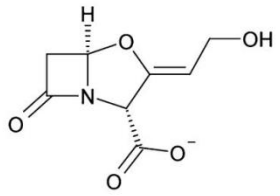
Approved by EMA 4/16

- Complicated intra abdominal infections;
- Complicated urinary tract infections and acute pyelonephritis
- documented infections due to ESBL-Enterobacteriaceae or P. aeruginosa that are susceptible to C/T

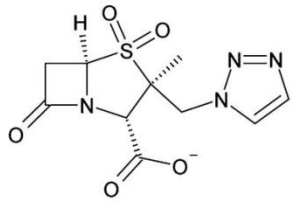
ß-lactamase inhibitors: novel agents

First generation: ß-lactam derivatives

- Clavulanic acid (AMX; Augmentin)
- Sulbactam (AMP; Unasyn)
- Tazobactam (PIP; Tazocin)



Clavulanic acid



Tazobactam

Novel generation: non ß-lactam inhibitors

(Diaza-bicyclo-octane (DBO), cyclic boronic derivatives

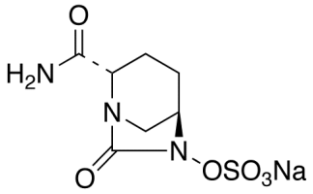
Table 1 | **Selected novel β-lactamase inhibitors in development**

Company	β-lactamase inhibitor (alternative name)	Partner antibiotic	Development stage
Actavis/AstraZeneca	Avibactam (NXL104)	• Ceftazidime • Aztreonam • Ceftaroline	• Ceftazidime–avibactam approved by the FDA in February 2015 • Aztreonam–avibactam and ceftaroline–avibactam are in Phase II
The Medicines Company	RPX7009	• Meropenem	• Phase III
Merck & Co.	Relebactam (MK-7655)	• Imipenem	• Phase II
Meiji Seika Pharma/ Fedora/Roche	OP0595 (RG6080)	• To be determined	• Phase I

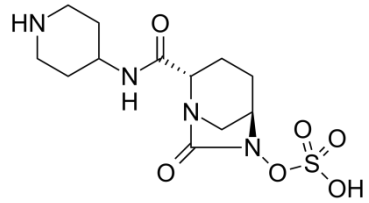
FDA, US Food and Drug Administration.

Nature Reviews Drug Discovery **14**, 445–447 (2015)

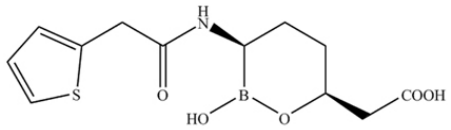
Avibactam



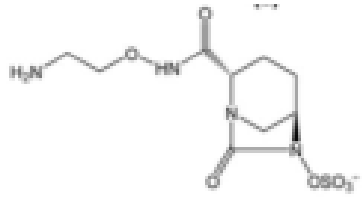
Relebactam



Vaborbactam (RPX7009)



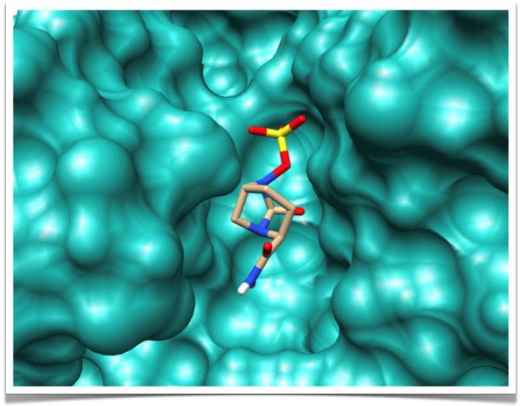
Nacubactam (RG6080)



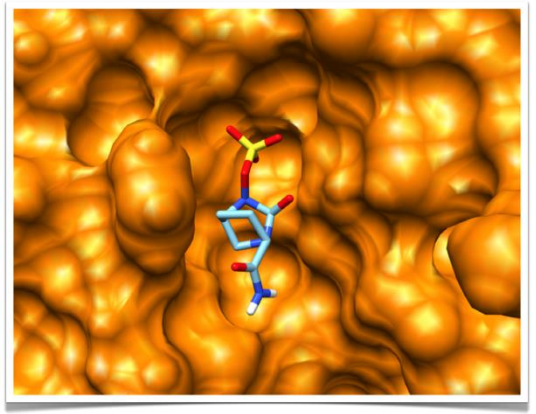
Existing ß-lactams in association with Avibactam (Old/new)

- In association with **ceftazidime (Zavicefta, Avycaz)**, ceftaroline or aztreonam (phase II)
- Ceftazidime /avibactam 2g/500 mg/8h
- Active against ESBL, AmpC and some CPE (KPC, OXA-48)
- **Inactive against MLBs (VIM, IMP, NDM)**
- No activity against Gram+ and anaerobes
- Phase 2 vs carbapenems in cIAI and cUTI
- Phases 3 completed in cIAI, cUTI, VAP, BGN cefta-R (clinicaltrials.gov)

Active Site KPC



Active Site OXA-48



Approved FDA 25 Feb 2015; Approved EMA ; 28 April 2016

- Comblicated intra-abdominal Infections;
- Complicated urinary tract infections (including pyelonephritis);
- Hospital acquired pneumonia (including VAP)
- Infection due to resistant Gram-neg with limted therapeutic options

Lucasti et al. JAC 2013, Riccobene et al. AAC 2013

Clinical efficacy of Ceftazidime/avibactam (Phase III Studies)

	Indication	Key Findings
I **Reclaim**	Complicated Intra-Abdominal Infections	• As effective as meropenem when combined with metronidazole in patients with cIAI
II **Recapture**	Complicated Urinary Tract Infections	• As effective as doripenem in patients with cUTI
III **Reprove**	Hospital Acquired Pneumonia, incl. Ventilator Associated	• As effective as meropenem in patients with HAP/VAP
IV **Reprise**	Pathogen directed (ceftazidime-R)	• Non-inferior to BAT in cIAI/cUTI caused by ceftazidime-resistant gram-negative pathogens (97% of patients were receiving carbapenem as BAT)

Ceftazidime / Avibactam – In vitro activity

Antimicrobial Activity of Ceftazidime-Avibactam Tested against Multidrug-Resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa* Isolates from U.S. Medical Centers, 2013 to 2016

94 US hospitals (2013-2016)
microdilution reference MIC method (CLSI)
Central laboratory
Susceptible breakpoint ≤ 8 µg/ml)

Almost exclusively KPC

	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	% S (CLSI)	% S (EUCAST)
Enterobacteriaceae (n=36,380)	**0.12**	**0.25**	**99.9%**	**99.9%**
MDR (ESBL) Enterobacteriaceae (n=2,953)	0.25	1	99.2%	99.2%
XDR Enterobacteriaceae (n=448)	0.5	2	97.8%	97.8%
CRE (n=513)	0.5	2	97.5%	97.5%
Colistin-R *K. pneumoniae* (n=205)	0.25	2	99.5%	99.5%
***P. aeruginosa* (n=7,868)**	**2**	**4**	**97.1%**	**97.1%**
MDR *P. aeruginosa* (n=1568)	4	16	86.5%	86.5%
XDR *P. aeruginosa* (n=717)	8	32	75.9%	75.9%
CAZ/MEM/PTZ –R *P. aeruginosa* (n=628)	8	32	71.8	71.8%)

H. Sader et al., AAC 2017

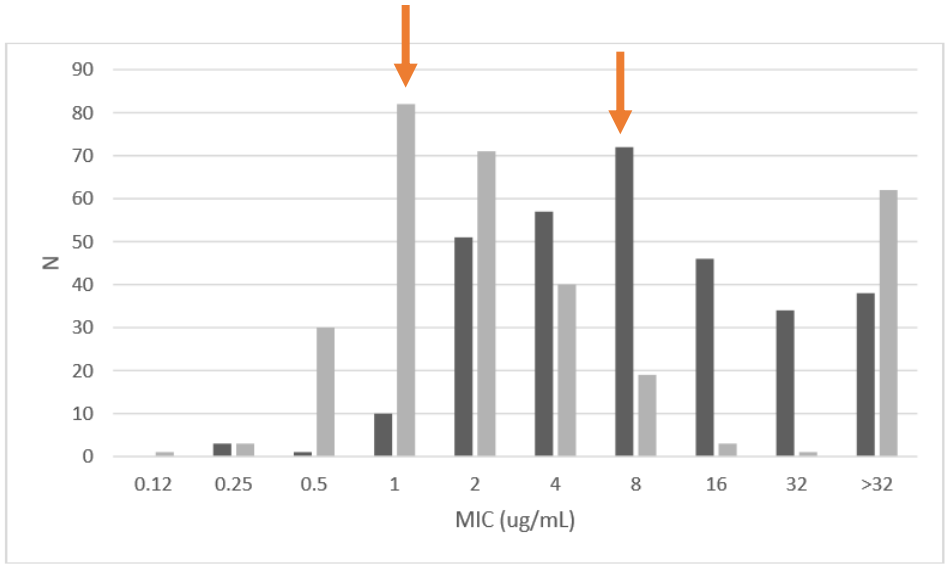
Microbiological comparison between ceftolozane-tazobactam and ceftazidime avibactam

	Ceftolozane-tazobactam	Ceftazidime-Avibactam
FDA indications	cIAI (with metronidazole) Complicated UTI (including pyelonephritis)	cIAI (with metronidazole) Complicated UTI (including pyelonephritis)
Gram-negative activity	*E. coli*, *E. cloacae*, *K. oxytoca*, *K. pneumoniae*, *P. mirabilis* *Pseudomonas aeruginosa*	*E. coli*, *E. cloacae*, *E. aerogenes*, *C. freundii*, *C. koseri*, *K. oxytoca*, *K. pneumoniae*, *P. mirabilis* *Pseudomonas aeruginosa*
Gram-positive activity	*Streptococcus anginosus*, *S. constellatus*, *S. salivarius*	NA
Anaerobic coverage	*Bacteroides fragilis*	NA
Beta-lactamase activity Class A (TEM, SHV, CTX-M, KPC) Class B (NDM, VIM, IMP) Class C (AmpC) Class D (OXA)	 Variable activity **(not on carbapenemases)** No activity Variable activity Active against OXA type ESBL (not OXA carba)	 **Active including carbapenemases (KPC)** No activity **Yes** Variable activity (yes **against OXA-48**)

Activity of ceftazidime/avibactam (CZA) and ceftolozane/tazobactam (C/T) against β-lactam resistant *Pseudomonas aeruginosa*

- Collection of 309 β-lactam-resistant* *P. aeruginosa* isolates (Los Angeles 2015-2016)
  (85% R to carbapenems, 75% R to Cefta/Cefep, 80% R to Pipt/tazo)

MIC distribution of C/T (grey bars) and CZA (dark) bars)



Overall: **73% S to C/T and 62% S to CZA**
(13% S to C/T only; 0.6% S to CZA only)

Table 2. Resistance profiles for *P. aeruginosa* isolates tested in this study

Resistance phenotype	N	%	S to CZA		S to C/T	
			N	%	N	%
R to ceftazidime	209	67.6	96	45.9	128	61.2
R to cefepime	149	48.2	48	32.2	77	51.7
R to imipenem	259	83.8	155	59.8	183	70.7
R to meropenem	228	73.8	118	51.8	149	65.4
R to TZP	183	59.2	94	51.4	128	69.9
R to ceftazidime & cefepime	145	46.9	44	30.3	73	50.3
R to imipenem & meropenem	220	71.2	117	53.2	145	65.9
R to ceftazidime, cefepime, imipenem, meropenem, TZP	105	34.0	29	27.6	55	52.4

CZA, ceftazidime-avibactam; C/T, ceftolozane-tazobactam; TZP, piperacillin-tazobactam

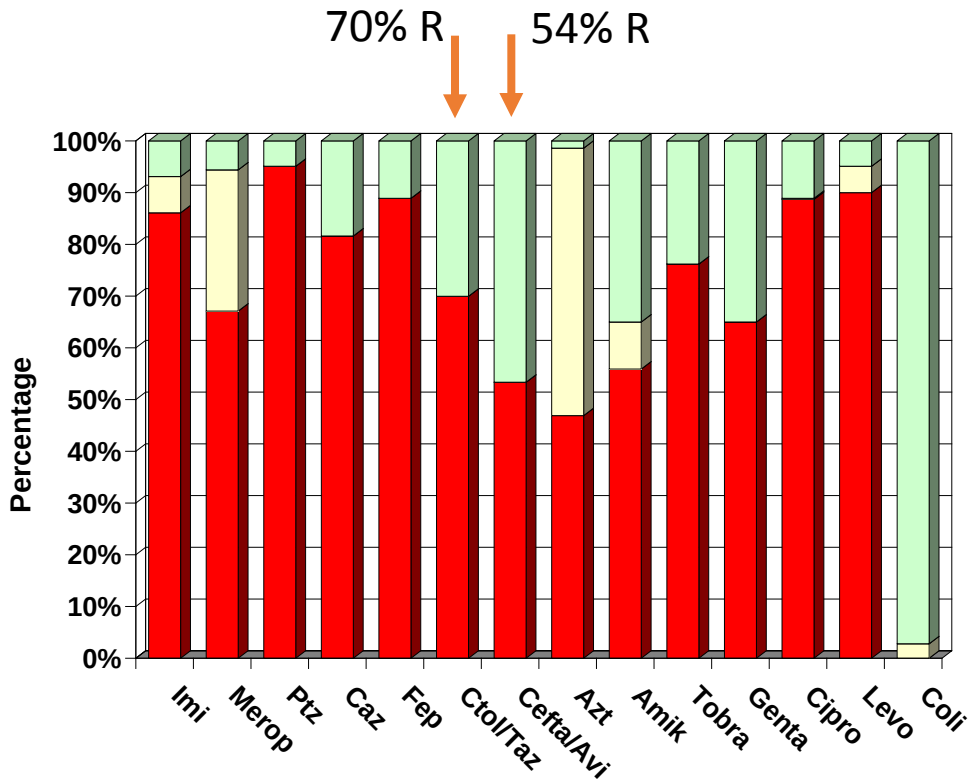
MDR/XDR

*Resistance to one or more agents: Ceftazidime, cefepime, imipenem, meropenem or pip/tazo

RM Humphries et al., AAC 2017

In vitro activity of CZA and C/T against MDR/XDR *P.aeruginosa* isolates in Belgian hospitals (2016)

MDR= resistant to ≥ 3 classes of ABs (penicillins, cephalos, carbapenems, aminoglycosides, FQ)



N=143 isolates
28 hospitals

Antimicrobial agents	MIC range (µg/ml)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)
Imipenem	1 - >256	32	>256
Meropenem	0.25 - > 256	32	>256
Piperacillin-tazob.	2 ->256	128	>256
Ceftazidime	0.5 - >256	32	128
Cefepime	1 ->236	32	128
Ceftolozane/tazob.	0.5 - >256	32	>256
Ceftazidime/avibactam	1-256	16	64
Aztreonam	0.25 - >256	32	128
Amikacin	1 ->256	32	128
Tobramycin	0.5 - >64	64	>64
Gentamicin	0.5 - >64	16	>64
Ciprofloxacin	0.12 - >64	16	>64
Levofloxacin	0.5 - >64	32	>64
Colistin	0.5 - 4	2	2

Overall: **48% MBL producers (VIM-2, VIM-4)**

Low activity of C/T and CZA against MDR/XDR P. aeruginosa

Y. Glupczynski et al., ECCMID 2017, Poster P2774

Ceftazidime-Avibactam:
From clinical trials to real-world setting

Outcomes with Ceftazidime-Avibactam in Patients with CRE Infections of any sources

60 pts – CRE infections
Retrospective review
Multicenter study
(USA, 2015-2016)
9 health systems
- 59% of patients in ICU
- 38% mechanical ventilation
- 40% moderate/severe renal disease
- 25% solid organ transplants

Median Charlson comorbidity Index: 4.5 (3-7)
Pitt's bacteremia score: 2 (0-5)
Mostly BSI and *Klebsiella pneumoniae* (KPC CRE)

Parameter	Patients, n/N (%)		
	In-hospital mortality	Microbiologic cure	Clinical success
Overall population	**19/60 (32)**	**39/60 (53)**	**39/60 (65)**
Treatment			
Concomitant therapy	9/27 (33)	17/27 (63)	17/27 (63)
Monotherapy	10/33 (30)	15/33 (45)	22/33 (67)
Location			
ICU	**16/35 (46)**	16/35 (46)	18/35 (51)
Non-ICU	3/25 (12)	16/25 (64)	21/25 (84)
Renal dose adjustment			
Yes	**14/33 (42)**	19/33 (58)	18/33 (55)
No	5/27 (19)	13/27 (48)	21/27 (78)
Infection type			
Bacteraemia	9/23 (39)	19/23 (82)	14/23 (61)
Urinary tract	2/17 (12)	7/17 (41)	15/17 (88)
Pneumonia (VAP)	**9/16 (56)**	7/16 (44)	9/16 (56)
Wound	2/8 (25)	3/8 (38)	5/8 (63)
Intra-abdominal	1/4 (25)	3/4 (75)	3/4 (75)
Bone/joint	1/2 (50)	1/2 (50)	0/2 (0)

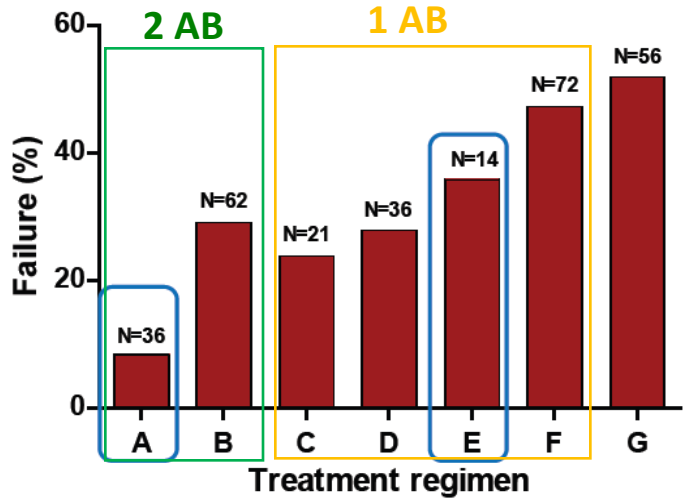
No control for confounding factors (retrospective study)

M. King et al. Antimicrob Agents Chemother 2017;61:e00449-17.

Treatment regimen for CPE

Outcome of 294 infections* caused by carbapenemase-producing *Klebsiella pneumoniae* according to treatment regimen.

34 studies (81% appropriate Rx on in vitro basis)



***70% bacteremias, 20% VAP+HAP**

- **Regimen A:** combination therapy with 2 active drugs one of which was a carbapenem with MIC ≤4μg/ml; **8.3%****
- **Regimen B:** combination therapy with 2 active drugs not including a carbapenem; **29%**
- **Regimen C:** monotherapy with an aminoglycoside; **24%**
- **Regimen D:** monotherapy with a carbapenem (MIC ≤4μg/ml); **25%**
- **Regimen E:** monotherapy with tigecycline; **35.7%**
- **Regimen F:** monotherapy with colistin; **47.2%**
- **Regimen G:** inappropriate therapy. **54%**

**** Failure rate**

A vs B p=0.02
A vs E p=0.03
A vs F p<0.0001
A vs G p<0.0001
B vs G p=0.014
C vs G p=0.04
D vs G p=0.03

Daikos GL, et al. Clin Microbiol Rev (submitted)

- MIC determination!
- Association with carbapenem (2-3 drugs) > monotherapy

Tzouvelekis et al., CMR 2012; 25: 682-707

Colistin vs. Ceftazidime-avibactam in the Treatment of CRE Infections: baseline characteristics

(prospective ?) **multicenter study**,
18 US hospital **(2012-2016)**
137 documented CRE infections
Colistin (2012-2016 period)
C/A (>2015-2016 period)

137 pts (**46% with BSI**)
133 pts **(97% K. pneumoniae CRE)**
KPC-2 (n=28; 52%), KPC-3 (n=24; 44%)
ST258A or ST258B clades

Characteristic	Patients, No. (%)[a] Ceftazidime-Avibactam (n = 38)	Colistin (n = 99)	All (N = 137)	*P* Value
Female sex	15 (39)	57 (58)	72 (53)	.06[b]
Age, median (IQR), y	57 (45–64)	63 (54–76)	61 (50–73)	.03[c]
Race/ethnicity				.71[b]
Black	14 (37)	42 (42)	56 (41)	
White	21 (55)	47 (47)	68 (50)	
Other	3 (8)	10 (10)	13 (9)	
Charlson comorbidity index, median (IQR)	2 (1–5)	3 (2–5)	3 (1–5)	.15[c]
Diabetes mellitus	18 (47)	42 (42)	60 (44)	.60[b]
COPD	5 (13)	27 (27)	32 (23)	.08[b]
History of malignancy	7 (18)	11 (11)	18 (13)	.24[b]
Immunosuppressed	11 (29)	14 (14)	25 (18)	.04[b]
Renal failure at admission	8 (21)	36 (36)	44 (32)	.09[b]
Renal failure at time of culture	11 (29)	44 (44)	55 (40)	.10[b]
Heart disease	14 (37)	50 (51)	64 (47)	.15[b]
Critical illness at time of culture[d]	7 (18)	40 (40)	47 (34)	.02[b]
Location at time of culture				.23[b]
Emergency department	6 (16)	20 (20)	26 (19)	
Intensive care unit	20 (53)	61 (62)	81 (59)	
Ward	12 (32)	18 (18)	30 (22)	
Time to culture, median (IQR), d[e]	3 (0–8)	2 (0–13)	2 (0–12)	>.99[c]
Origin				.40[b]
Home	18 (47)	36 (36)	54 (39)	
Hospital transfer	7 (18)	15 (15)	22 (16)	
Skilled nursing facility	11 (29)	35 (35)	46 (34)	
Long-term acute care	2 (5)	13 (13)	15 (11)	
Type of infection				.59[b]
Bloodstream	15 (39)	48 (48)	63 (46)	
Pneumonia	9 (24)	21 (21)	30 (22)	
Urinary tract	6 (16)	13 (13)	19 (14)	
Wound	6 (16)	8 (8)	14 (10)	
Other	2 (5)	9 (9)	11 (8)	
Type of CRE				>.99[f]
Klebsiella pneumoniae	37 (97)	96 (97)	133 (97)	
Enterobacter sp.	1 (3)	3 (3)	4 (3)	
Susceptibility (susceptible/tested)				
Colistin	23/30 (77)	63/68 (93)	86/98 (88)	.04[f]
Ceftazidime-avibactam	18/19 (95)	5/5 (100)	23/24 (96)	>.99[f]

D. van Duin et al. Clinical Infectious Diseases, 2017

Colistin vs. Ceftazidime-avibactam in the Treatment of Infections due to Carbapenem-R Enterobacteriaceae

Figure 1.A. ceftazidime-avibactam (n=38)

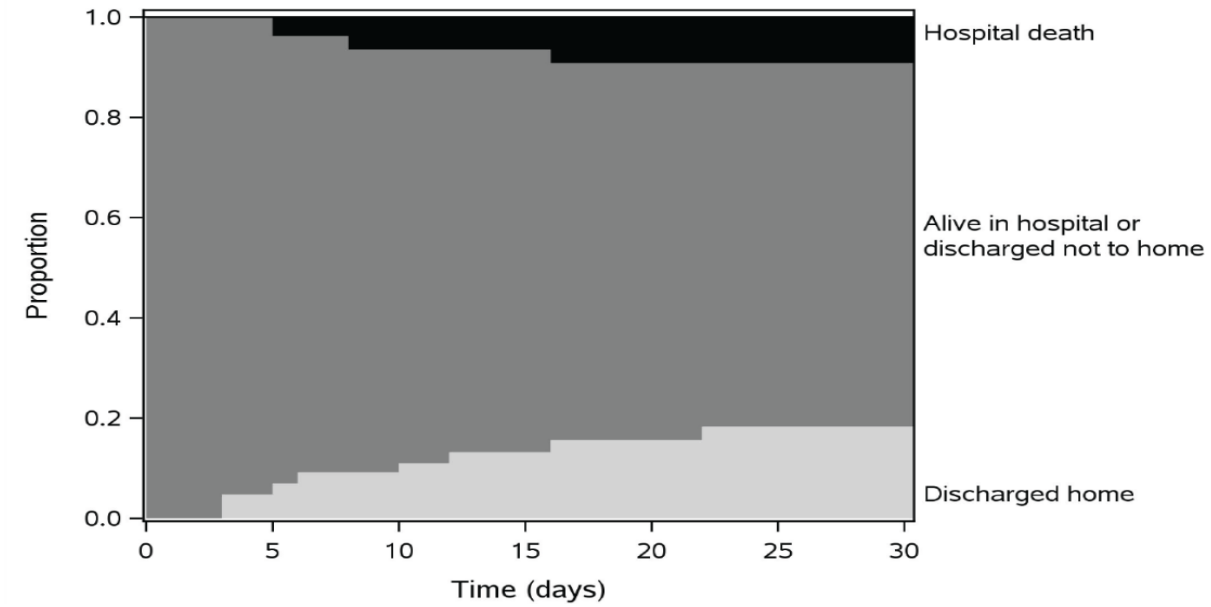
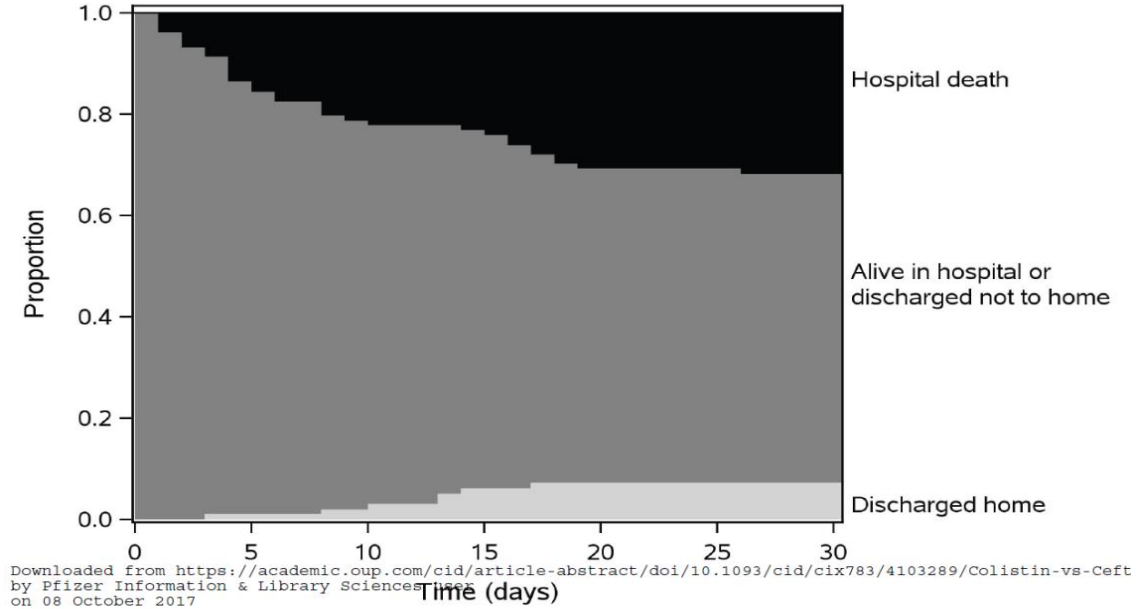


Figure 1.B. colistin (n=99)



N=137, **adjusted all cause mortality at 30 days: ceftaz/avibactam 9% vs colistin (32%); diff 23%** (95% CI, 9%–35%; P= .001)

Adjustment for potential confounding by IPTW (covariate in model; charlson score, Pitt score (<4 or ≥4), type of infection (BSI vs UTI vs other), Age groups, Creatinine level (≥ 2 mg/L at the time of first positive culture)

A. ceftazidime-avibactam group (n=38). B. colistin group (n=99).

Loading/daily Dose of colistin not specified (variation over time ? Comparable to currently used posology for CRE infection ?)

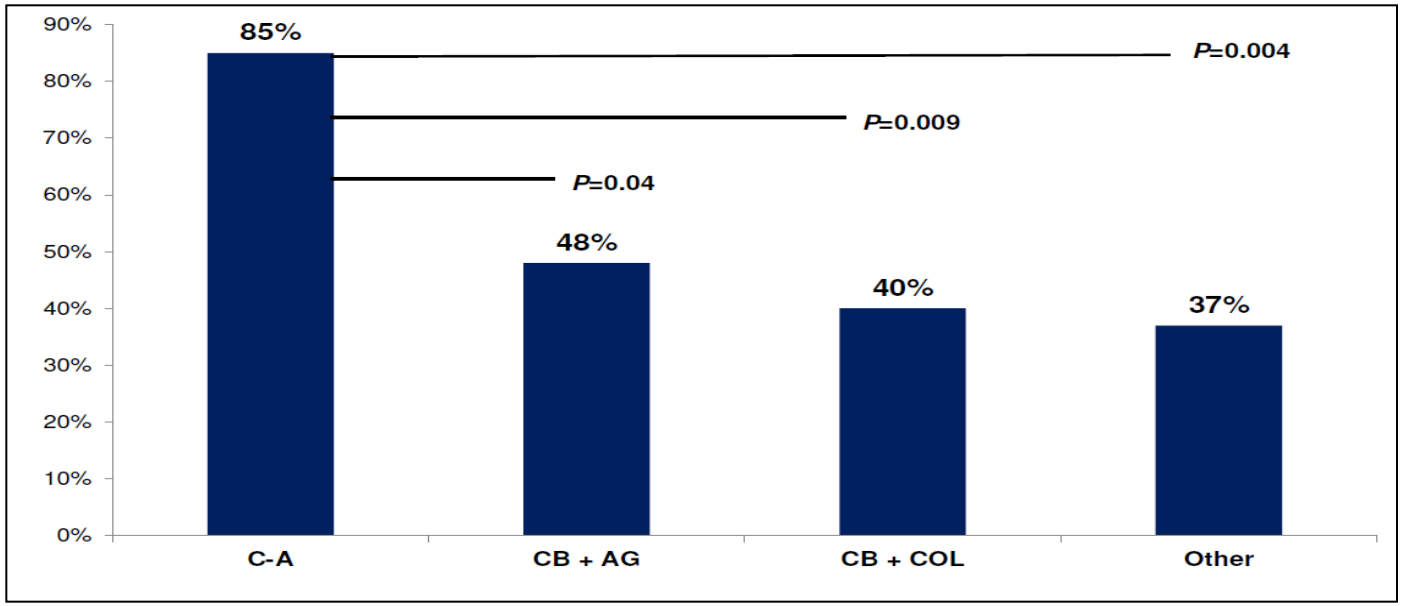
D. van Duin et al. Clinical Infectious Diseases, 2017

Superiority of Ceftazidime–avibactam to other treatment regimens in CRE *Klebsiella pneumoniae* bacteremia (n=109 cases; 97% KPC-K. pneumoniae)

Retrospective study, single centre (USA: 2009-2017). Groups comparable: age, underlying diseases (SOT, immunosuppressed), severity of illness, proportion/types of primary/secondary bacteremia; proportion ICU patients; strain characteristics (KPC-2/-3)

Rates of 30-day clinical success across treatment regimens

Combination therapy of C-A with gentamicin (5d) in 5/13 (38%) patients



Small sample sizes
Not RC trial
Investigators not blinded
(posible selection bias in therapy)

Higher 90-days survival rate in C-A group (92%) vs others (CARB+AG (56%), CARB+ COL ((%) or Other regimens (monotherapy or combinations without CARB) (49%)
Lower rate of acute kidney injury in C/A group at end of treatment(18%) vs CARB+AG (44%) and CARB + COL (57%)

C-A, ceftazidime–avibactam; CB+AG, carbapenem and aminoglycoside; CB+COL, carbapenem and colistin; CRE, carbapenem-resistant Enterobacteriaceae.

Shields RK, et al. *Antimicrob Agents Chemother* 2017. doi:10.1128/AAC.00883-17.

Clinical outcomes and emergence of ceftazidime–avibactam resistance among patients treated for CRE infections

Single centre experience University hospital, Pittsburgh, (2015-2016): CRE infections (Tx ≥ 3 days C/A; dose 2.5 IV q8h, adjustment for renal failure)

- 37 patients; mean age 64 years old; 30% transplant recipients
- 12 pneumonia, 10 bacteremia
- **Ceftazidime–avibactam monotherapy 70%**
  - 30-day survival 76% (**cure with no recurrence of infection in 59% of patients**)
  - 90-day survival 62%
- **Clinical Failure:** 15 pts; **(41%)**
  - Death (n=9); recurrence (n=4); no clinical improvement (n=2)
- **Microbiologic failure:** 10 pts **(27%)**
  - **Emergence of resistance during Tx in 3 patients (30% of failures; 8% of total)** (after 10–19 days of treatment)

Shields et al. Clinical Infectious Diseases 2016;63:1615–1618.

Mechanisms of resistance to ceftazidime/avibactam

- In KPC-3 (20x higher catalytic efficiency than KPC-2 against ceftazidime). Ceftazidime MICs 10x higher for KPC-3 vs KPC-2
- KPC-3 variants observed in vitro and during CAZ/AVI treatment (Carbapenemases-> ESBL); <-> selection of mutations in the KPC Ω loop active site
  - D179Y (Asp-> Tyr) mutation -> increase by 100-1000x hydrolysis of ceftazidime (selection in vitro upon exposure to CAZ/AVI conc. 16x MIC value (frequencies of 10^{-9})
- Increased expression of KPC-3 (transposition of KCP Tn4401 transposon in a second plasmid (higher copy number genes)
- mutations in OmpK36 porin -> decreased membrane permeability to CAZ/AVI

NB: Cefepime/carbapenem treatment-> selection pressure for mutations in OmpK36 porin (Klebsiella spp., Enterobacter spp.)

Livermore et al. AAC 2015
Compaire et al. AAC 2017
Haisdar et al., AAC 2017
Humphries et al AAC 2017

Aztreonam / Avibactam

- Aztreonam hydrolyzed by many serine β-lactamases (Class A: ESBL, KPC) but not by MBLs (Class B)
- Combination AZT/Avibactam-> improved activity against MDR including carbapenemases (KPC, MBLs, OXA-48)
- MIC_{90} of AZT/AVIB (4 mg/L)= 0.12 µg/ml for all Gram-negative in a large US survey; 99,9% susceptibllity overall (most CRE with MIC $\leq$ 2 µg/ml)
- Less active against MDR *P. aeruginosa* isolates (MIC90: 32-64 µg/ml); No activity against *A. baumannii*

Clinical data

- Phase II clinical trial in cIAI ongoing (pharmacokinetics, safety, tolerability)
- Sucessful outcomes in small number of patients treated by combination Cefta/Avi + Aztreonam for MDR gram-neg (NDM-CRE, carbapenem-resistant *P. aeruginosa*,….) (compassionate usage, no randomized controlled trial)

Aztreonam / Avibactam – In vitro activity

***In Vitro* Activity of Aztreonam-Avibactam against *Enterobacteriaceae* and *Pseudomonas aeruginosa* Isolated by Clinical Laboratories in 40 Countries from 2012 to 2015**

stability against MDR (including Class B besides Class A and class D (some)

>50000 isolates
208 hospitals, 40 countries worldwide (2012-2015)
microdilution reference MIC method (CLSI)
Central laboratory
Susceptible CLSI breakpoint ≤ 4 µg/ml)

	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	MIC Range (µg/ml)	% S (CLSI)
Enterobacteriaceae (n=51,352)	**0.06**	**0.12**	**0.015->128**	**99.9%**
Meropenem-R Enterobacteriacae (n=1;498)	0.25	1	0.015-32	99.8%
Meropenem-R, non MBL (n=1,248)	0.25	1	0.015-32	99.2%
Meropenem-R, MBL positive (n=250)	0.12	1	0.015-8	97.8%
***P. aeruginosa* (n=11,842)**	**8**	**32**	**0.06->128**	**73.4%**
MBL-positive (n=452)	16	32	0.25->128	38.1%

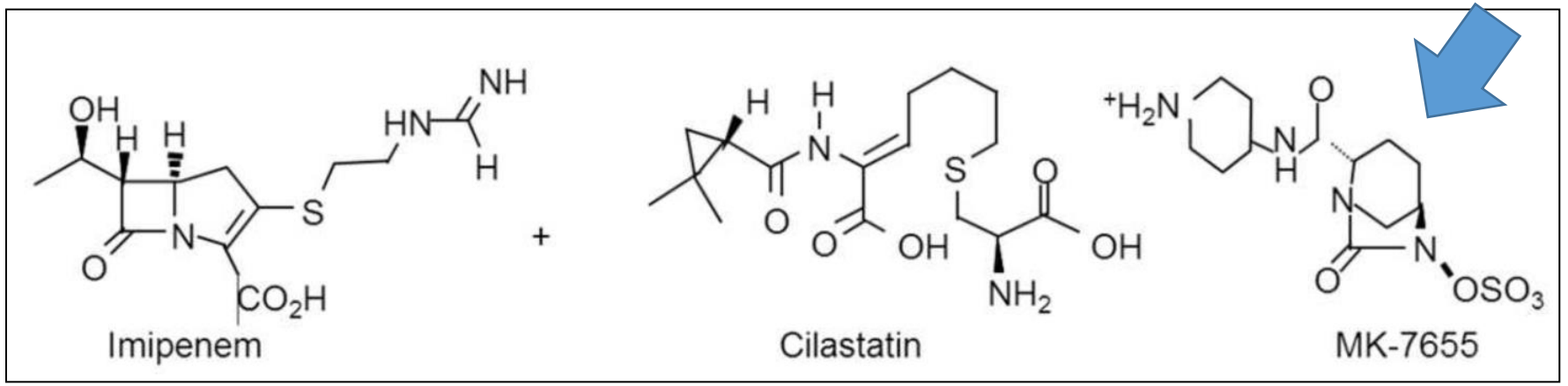
For Enterobacteriaceae, MIC_{90} Aztr/Avi = 0.12 µg/ml (vs Aztr = 64 µg/ml)
99.8% of all meropenem-R Enterobacteriaceae inhibited at MIC ≤ 8 µg/ml
MBL CPE producers: MIC_{90} of 1 µg/ml
For P. aeruginosa, MIC_{90} Aztr/Avi= 32 µg/ml (vs Aztr MIC= 64 µg/ml)

J.A Karlowsky et al., AAC 2017

Imipenem/Relebactam (MK-7655)- Merck

- **Irreversible inhibitor of class A (ESBL, KPC) and Class C (AmpC) β-lactamases**
  (64-fold decrease of imipenem MICs in KPC producing Klebsiella pneumoniae)
- **Good activity against AmpC overproducing *P. aeruginosa***
  (imipenem MICs decreased 8x from >16 µg/ml to 2 µg/ml)
- Not active against class B (VIM, NDM), not active against class D (OXA-48)
- Little/no activity against MDR *A. baumannii* (OXA-23 !)

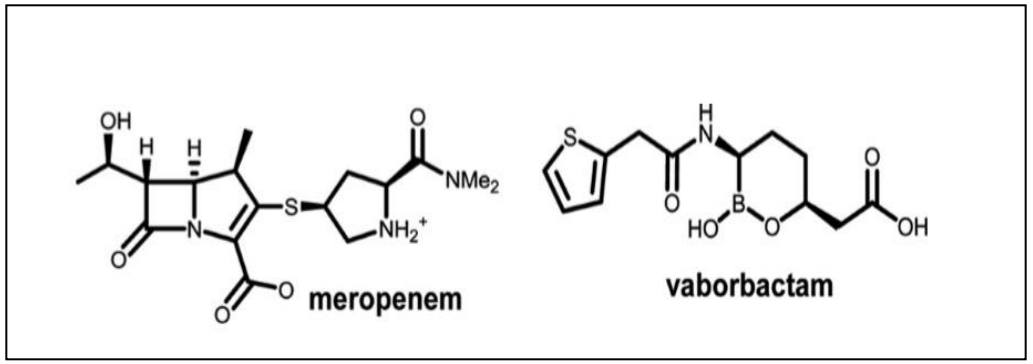
Diazabicyclooctane (DBO)
Piperidine analogue



Imipenem/Relebactam – Clinical studies

- Dosage IMI/REL 500mg/250 mg /6h (optimal dosage found in Phase II studies, to be confirmed in phase 3 studies)
- Phase 2: cUTI and cIAI non inferiority obtained to comparators (PTZ or IMI), similar profiles/proportions of AEs
- Phase 3: ongoing
  - Nosocomial pneumonia (HABP or VABP) evaluation of IMI/REL vs Pip Tazo
  - CRE Infections with isolates IMI R & coli S -> IMI/REL regimen vs IMI + colistine

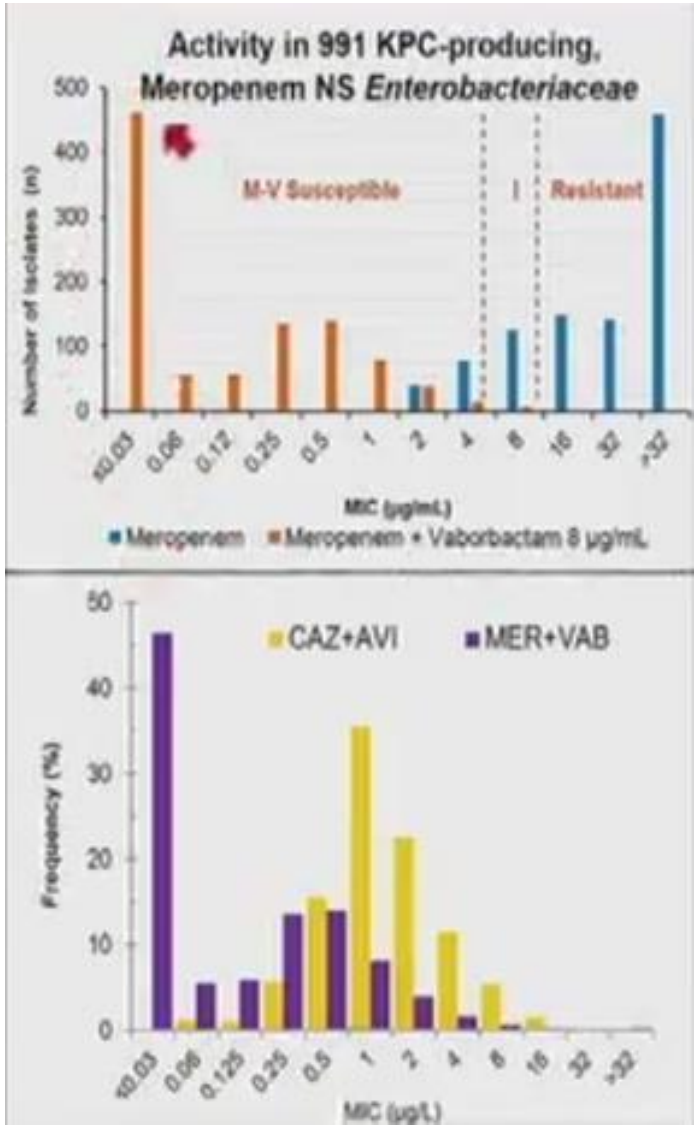
Meropenem/Vaborbactam
(Vabomere®, Medicine company)



- Vaborbactam: novel cyclic boronic acid inhibitor of β-lactamases (class A, and C); does not inhibit class B (NDM, VIM) nor class D (OXA-48)
- Reversible inhibitor; covalent binding of boro moiety and serine hydroxyle active site of β-lactamases (prolonged binding to KPC enzyme +/- 1000 min vs 77 min for avibactam)
- No intrinsic antibacterial activity
- Varbobactam (8 µg/ml) restores activity of meropenem (MIC ≤ 2 µg/ml) against KPC producing CRE (16-32 x fold decrease in MICs); Active against KPC-3 isolates that are R to avibactam (<D179Y mutation in KPC)
- No activity against MDR *P. aeruginosa* nor against *Acinetobacter* spp

In vitro activity of vaborbactam

- Restores activity of meropenem in KPC-producing CRE (modal MIC ≤0.03 µg/ml vs 1 µg/ml for C/A)
- Breakpoints for Enterobacteriaceae:
  Susceptible ≤ 4 µg/ml; Intermediate: 8 µg/ml
  Resistant ≥ 16µg/ml
- No change in meropenem acitivity in *P. aeruginosa* or *Acinetobacter* spp. due to efflux/low permeability



Adapted from M. Dudley, IDWeek 2017

Meropenem/Vaborbactam

- **Pharmacologic properties** (well adapted for combination with penems):
  - Excretion in urine unchanged (Meropenem: 50%; vaborbactam: 75-95%)
  - No hepatic elimination
  - Half life elimination: +/- 1.5 h (same for Mero and varbobactam)
  - Low serum protein binding (Mero 2%; varbobactam 30%)
  - Adjustment in case of renal impairment as for meropenem alone
    (renal insufficiency similarly affects pharmacology of the 2 drugs)

- **Clinical indications** **(Status: FDA approved for cUTIs and pyelonephritis on August 29, 2017)**
  - Complicated UTI including acute pyelonephritis (caused by (CRE) Enterobacteriaceae susceptible to M/V (E. coli, Klebsiella, Enterobacter)
  - Dosage 2g/2g IV (3 hr infusion)/8h for ≤ 14 days

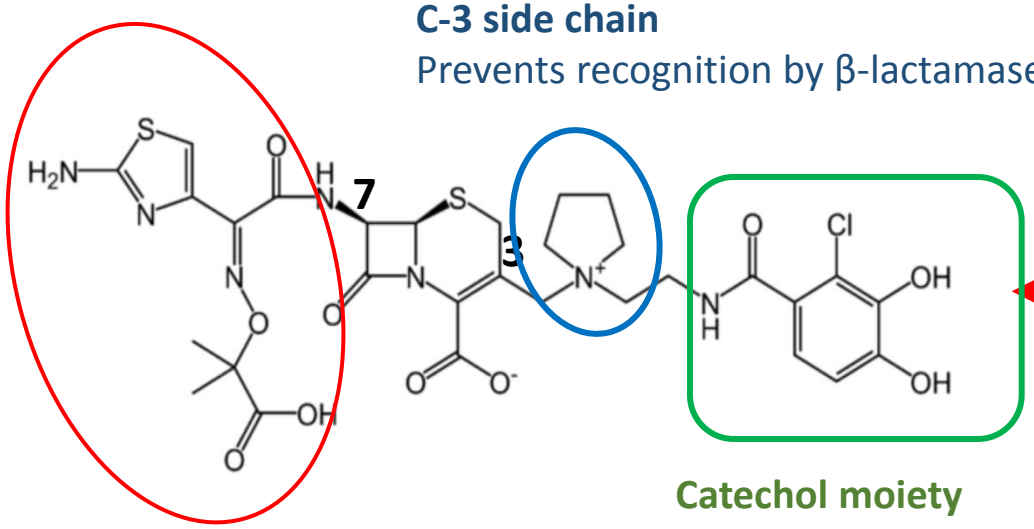
Meropenem-Varbobactam clinical phase 3 studies

- Prospective, RCT monotherapy with M/V vs. Best available Therapy in suspected or documented CRE infections
- Improved outcome with meropenem-vaborbactam compared to BAT:
  - **Reduced mortality**
  - **Higher clinical cure at EOT and TOC**
  - **Benefit shown in sefveral patient subgroups** (HABP/VABP, bacteremia, renal impairment and immunocompromised)
  - **Reduced AEs** (lower nephrotoxicity in M/V group)
  - **No change in susceptibility to M/V during/after treatment**

From M Dudley, ID Week 2017

Cefiderocol (S649266) - Shionogi

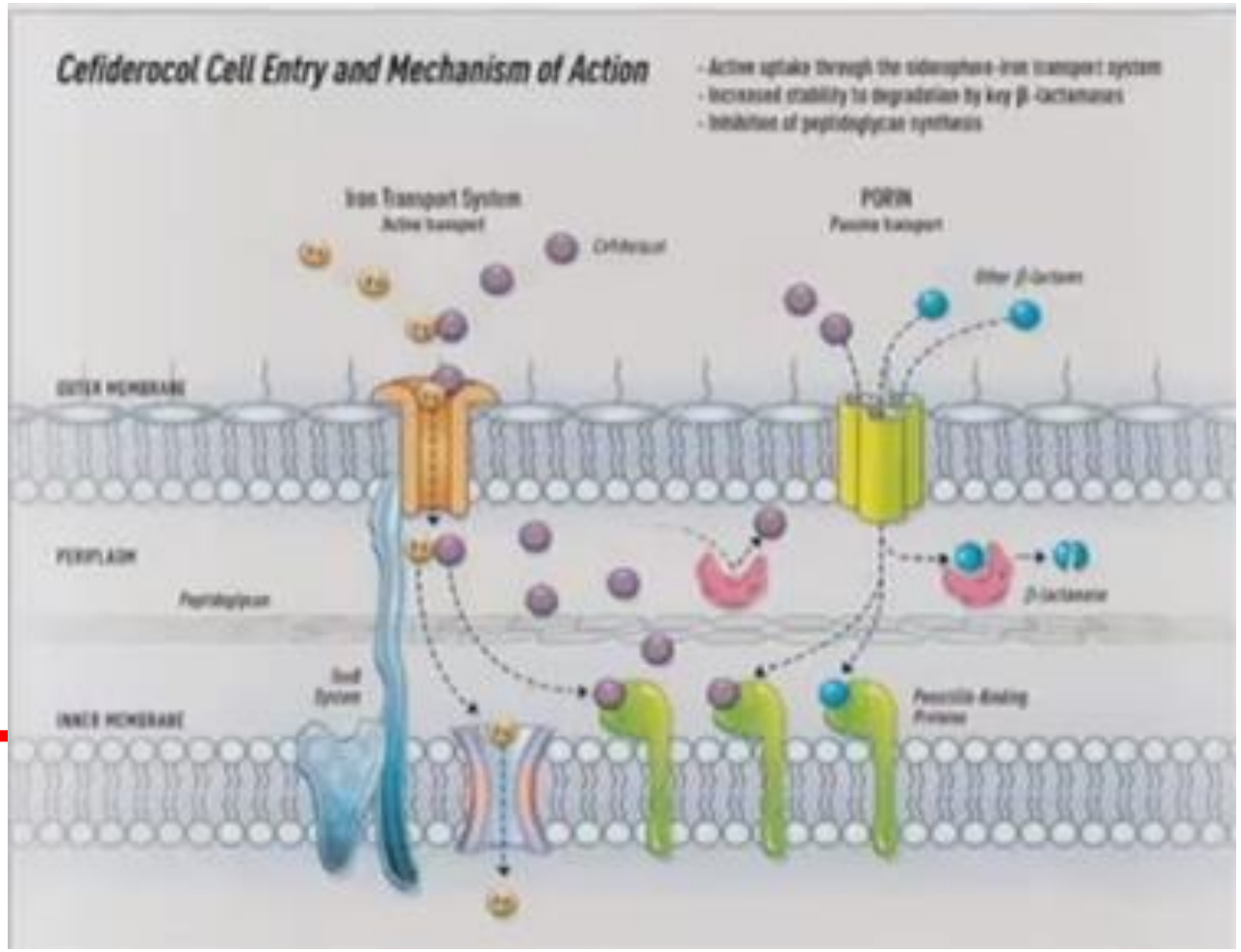
- Siderophore Cephalosporin



C-3 side chain
Prevents recognition by β-lactamases

C-7 side chain
enhances stability against β-lactamases

Catechol moiety
Additional stability against β-lactamases
Binds to ferric iron ions



High stability and R to β-lactamase and **rapid active uptake through the siderophore ferric iron transport system** (almost not affected by classical efflux pump systems)

Cefiderocol : in vitro activity

Active against MDR Enterobacteriaceae (CRE), *P. aeruginosa*, *Acinetobacter* spp. and *S. maltophilia*

In Vitro Activity of the Siderophore Cephalosporin, Cefiderocol, against a Recent Collection of Clinically Relevant Gram-Negative Bacilli from North America and Europe, Including Carbapenem-Nonsusceptible Isolates (SIDERO-WT-2014 Study)

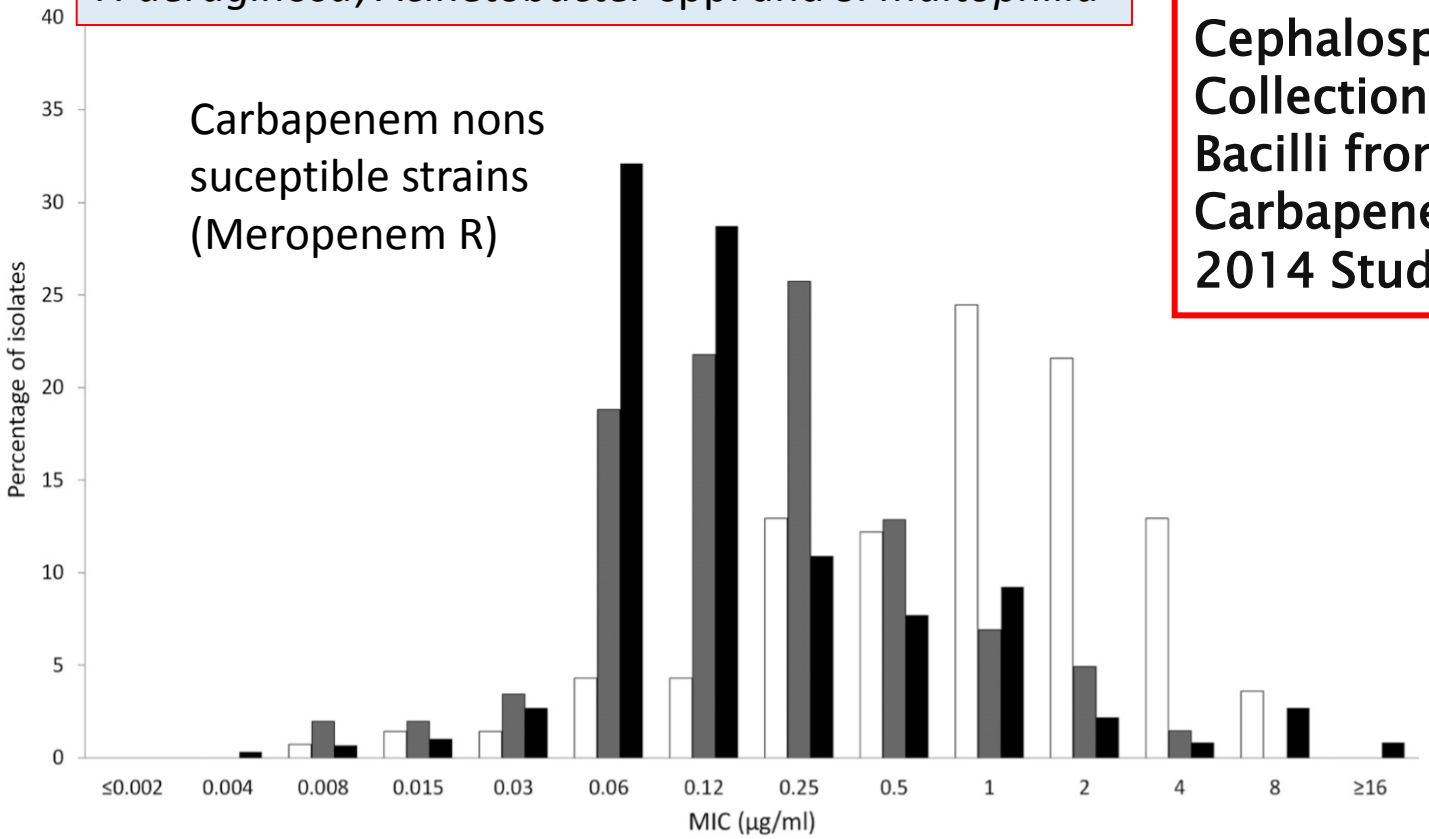


FIG 2 Cefiderocol MIC distributions for meropenem-nonsusceptible *Enterobacteriaceae* (white bars; $n = 139$), *P. aeruginosa* (gray bars; $n = 202$), and *A. baumannii* (black bars; $n = 595$) isolates collected by European medical center laboratories.

MIC90: 0.5-1 µg/ml for Enterobacteriaceae, *P. aeruginosa* and *A. baumannii*

99.6% of all strains *inhibited at ≤ 4 µg/ml of cefiderocol*

98.3% of Mero-R strains (n=1718) inhibited at ≤ 4 µg/ml of cefiderocol

M. Hackel et al., AAC 2017; 61 (9 e00093-17)

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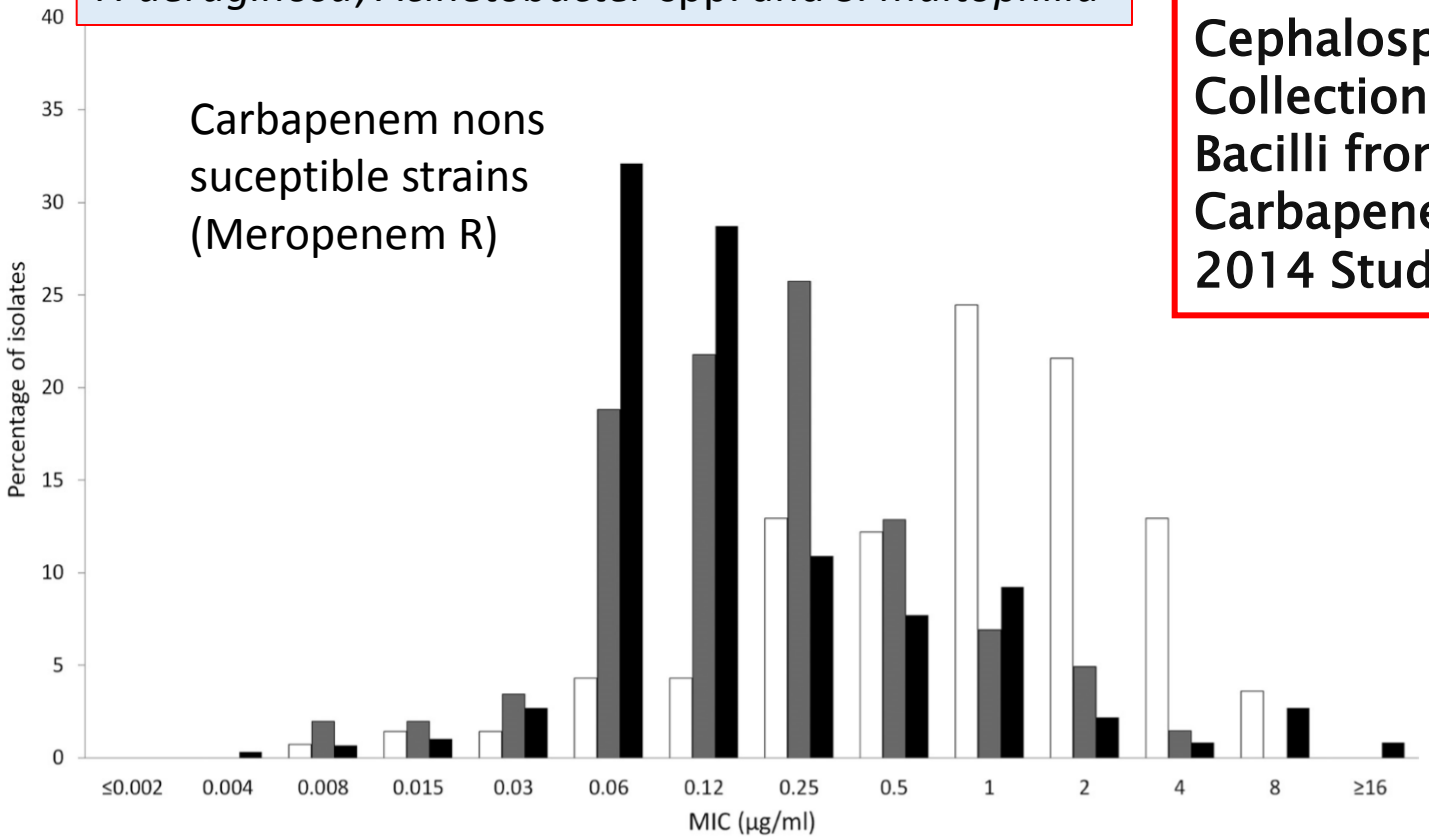

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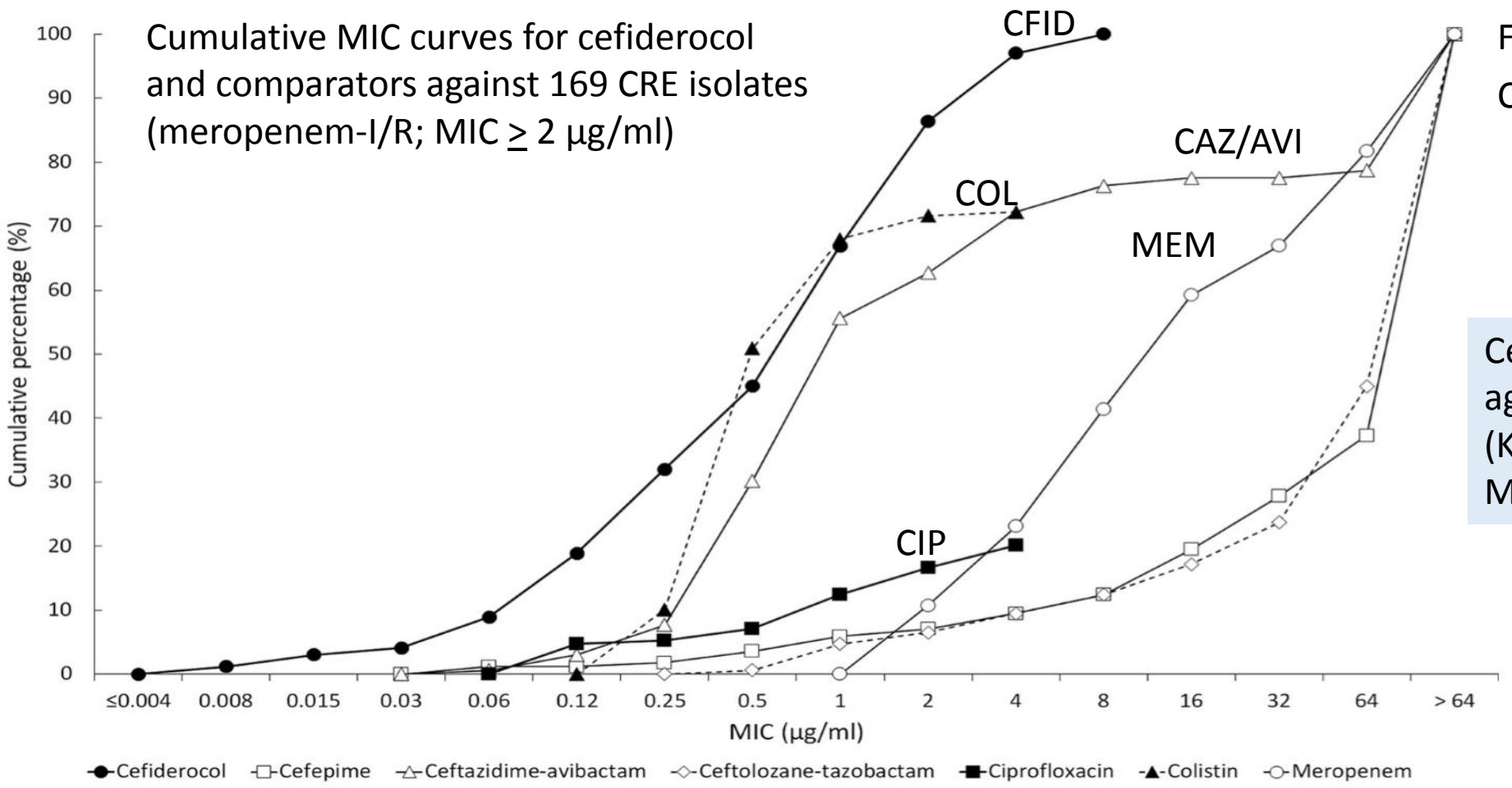
Cefiderocol: in vitro activity against CRE

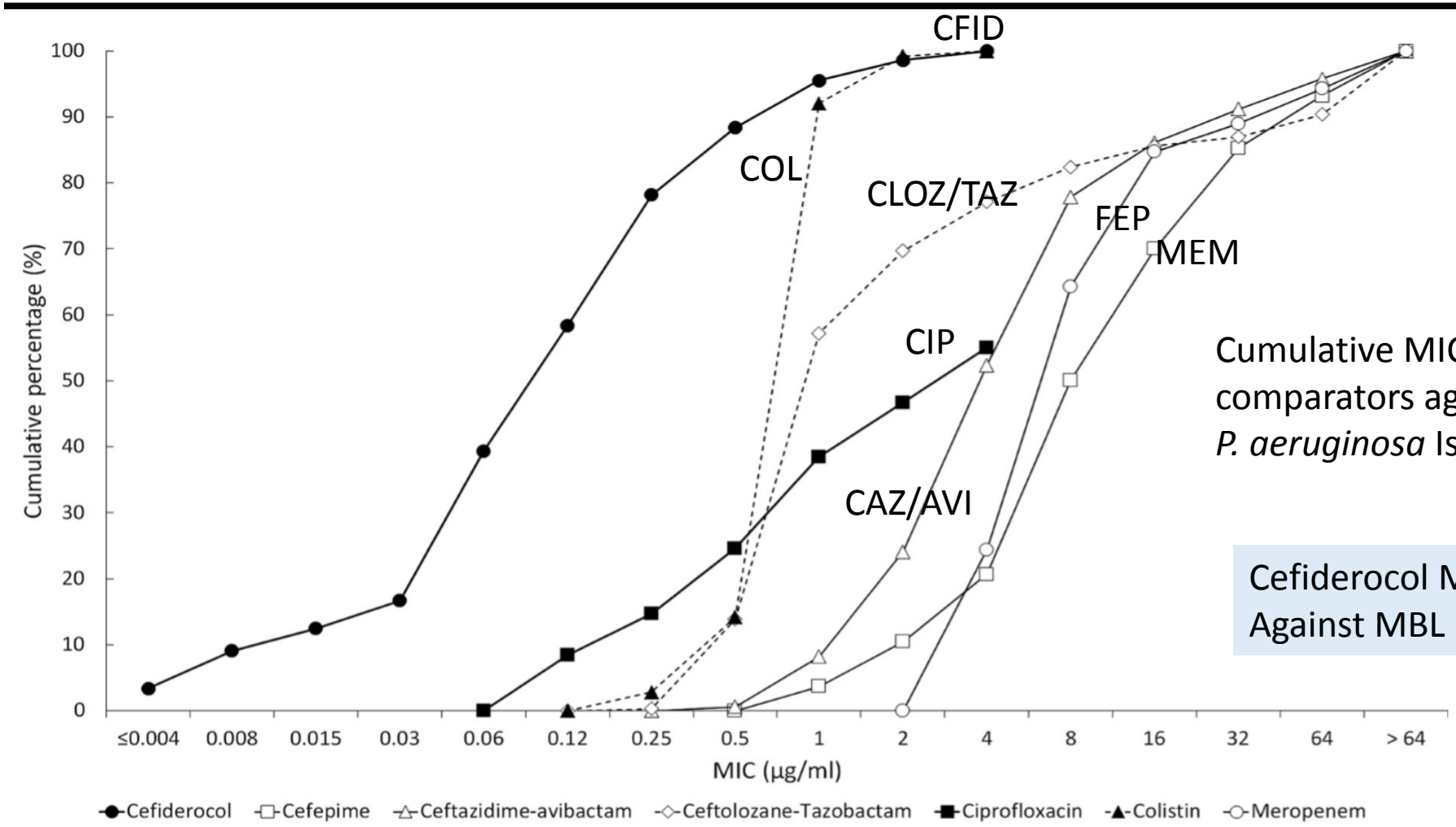


Cefiderocol is active against all CRE types (KPC, NDM, VIM, IMP, OXA-48) MIC: ≤0.125 to 4 µg/ml)

FIG 3 Cumulative MIC susceptibility curves for cefiderocol and comparators against 169 meropenem nonsusceptible *Enterobacteriaceae* from North American and European medical center laboratories. For colistin and ciprofloxacin, the endpoint of their respective cumulative MIC susceptibility curves represents the highest concentration tested. The remaining tested isolates had MICs higher than their endpoint value.

M. Hackel et al., AAC 2017; 61 (9 e00093-17)

Cefiderocol: in vitro activity against *P. aeruginosa*



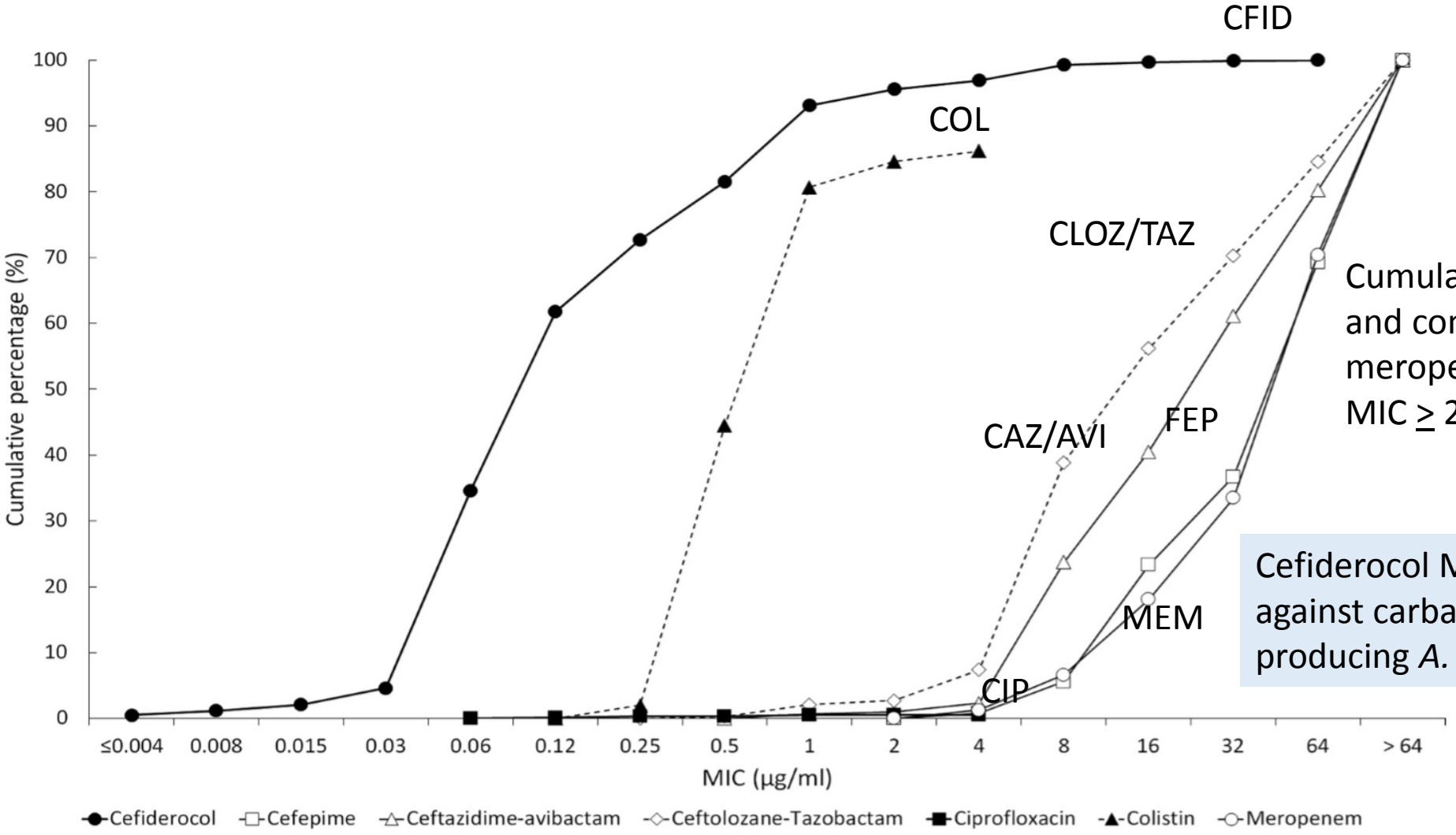
Cumulative MIC for cefiderocol a nd comparators against 353 meropenem I/R *P. aeruginosa* Isolates MIC $\geq$ 2 µg/ml)

Cefiderocol MIC_{90} of 4 µg/ml
Against MBL producing *P. aeruginosa*

FIG 4 Cumulative MIC susceptibility curves for cefiderocol and comparators against 353 meropenem-nonsusceptible *P. aeruginosa* isolates from North American and European medical center laboratories. For colistin and ciprofloxacin, the endpoint of their respective cumulative MIC susceptibility curves represents the highest concentration tested. The remaining tested isolates had MICs higher than their endpoint value.

M. Hackel et al., AAC 2017; 61 (9 e00093-17)

Cefiderocol: in vitro activity against *A. baumannii*



Cumulative MIC curves for cefiderocol and comparators against 768 meropenem I/R *A. baumannii* isolates MIC ≥ 2 µg/ml)

Cefiderocol MIC_{90} of 8 µg/ml against carbapenemase (OXA-23, OXA-58) producing *A. baumannii*

FIG 5 Cumulative MIC susceptibility curves for cefiderocol and comparators against 768 meropenem-nonsusceptible *A. baumannii* isolates from European and North American medical center laboratories. For colistin and ciprofloxacin, the endpoint of their respective cumulative MIC susceptibility curves represents the highest concentration tested. The remaining tested isolates had MICs higher than their endpoint value.

M. Hackel et al., AAC 2017; 61 (9 e00093-17)

Cefiderocol vs Imipenem in acute cUTI (APEKS)

452 hospitalized pts with cUTI; (immunocompromised pts; number of uncomplicated acute pyelonephritis limited to <30%)
Cefiderocol vs Imipenem administration for 7-14 days (median= 9 days)
E. Coli/Klebsiella = primary pathogens (> 50% cefepime I/R in the cefiderocol aerm)

- Response at test of cure in microbiological intent-to-treat population

	Cefiderocol N (%)	Impenem/Cil N (%)	Adjusted Δ (%)	95% CI
# Patients	252	119		
Clinical + Micro*	183 (72.6%)	65 (54.6%)	28.9%	8.23%, 28.92%
Clinical	226 (89.7%)	104 (87.4%)	2.4%	-4.66%, 9.44%

* Primary endpoint (composite outcome at TOC in mMITT population)

Porsmouth et al. IDWEEK 2017, abstract 1869

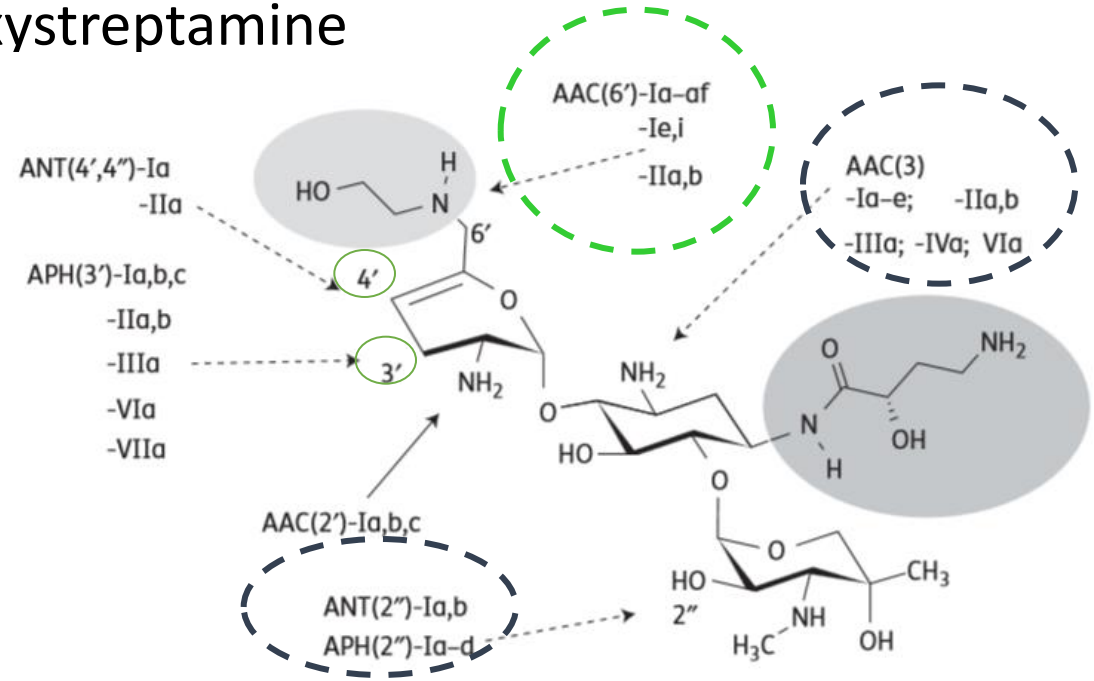
Cefiderecol - Clinical Development program

	APEKS-cUTI	APEKS-NP	CREDIBLE-CR
Feature	Site/Indication focus US Pivotal	Site/Indication focus US Pivotal	Pathogen focused Europe pivotal
Patients	cUTI/AUP	**Nosocomial pneumonia HAP/VAP**	**cUTI, HAP/VAP/HCAP, BSI/Sepsis due to CR GNB**
Design	Randomized 2:1 Double-blind	Randomized 1:1 Double-blind	Randomlized 2:1 Open-label
Comparator	Imipenem/Ciliastatin	Meropenem	« Best Available Therapy »
Status	Completed	Ongoing	Ongoing

APEKS = **A**cinetobacter, **P**seudomonas, **E**. coli, **K**lebsiella, **S**tenotrophomonas

Plazomicin - Achaogen

- Aminoglycoside (derivative of sisomicin (gentamicin B))
  - Hydroxy-ethyl group in 6’ position
  - Hydroxy-aminobutyric acide(HAB) in position 1 of 2-deoxystreptamine



Sterical hindering

Figure 1. Structure of ACHN-490. The hydroxyethyl (circled, light grey) at 6′ blocks AAC(6′)-I and -II, and the 1-*N*-hydroxyaminobutyric acid (also circled, dark grey) blocks AAC(3), ANT(2″) and APH(2″). The lack of hydroxyls at 3′ and 4′ prevents modification by APH(3′) and ANT(4′,4″). The compound remains vulnerable to AAC(2′)-Ia, -Ib and -Ic, but these are chromosomal enzymes unique to *Providencia* spp.

Only active AME = AAC(2’) (*Providencia*. spp)
Activity affected by ARN16S methylases

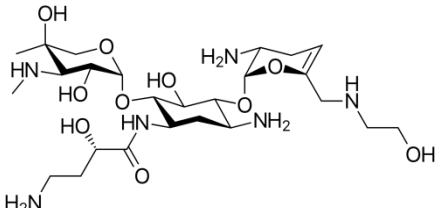
Livermore et al., JAC 2011

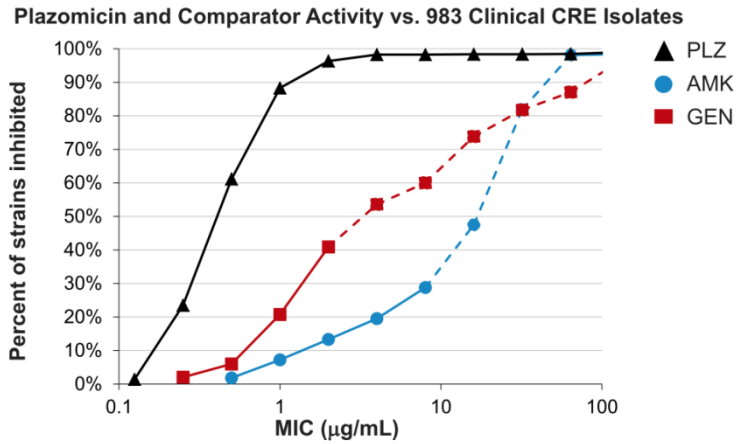
Plazomicin - Achaogen

- Active against isolates resistant to other AGs (genta, tobra, amika-R;
- Active against all AG modifying enzymes (AME) except AAC(2')-Ia, -Ib, -Ic (++ *Providencia*) and against 16S ARN methylases (NDM CRE)
- Active against AmpC, ESBL, CRE (KPC)
- Inactive vs NDM
- Active against *S. aureus*, coag neg Staphylococci
- limited activity against *Acinetobacter,*

S. pneumoniae, Enterococcus sp.

- Half-live: 4 hrs
- renal excretion: 87%
- Phase III in cUTI, CRE infections (combination
- less nephrotoxicity, cochleovestibular





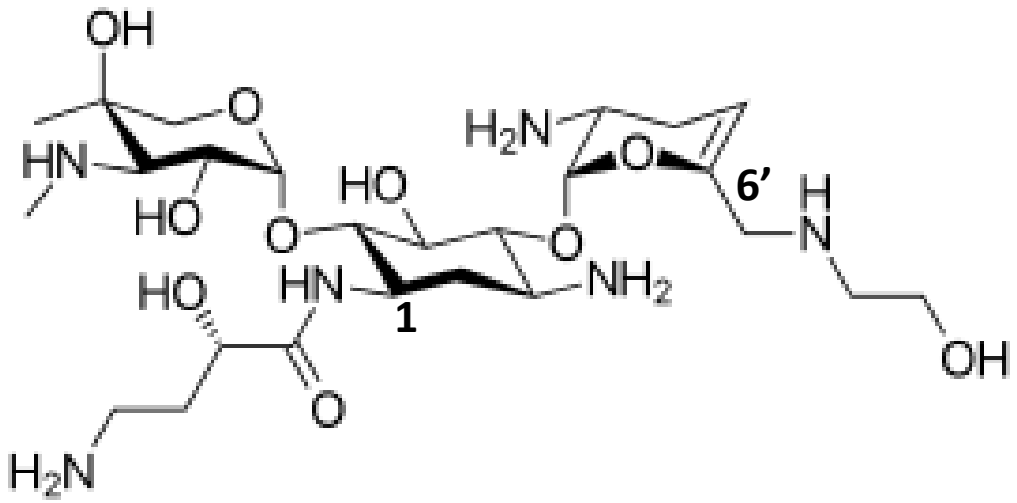
N=983 Enterobacteriaceae isolates with an MIC ≥4 µg/mL for any type 2 carbapenem; dashed line indicates non-susceptible via EUCAST breakpoints

Enzymes produced (no. isolates)	MIC (mg/L) ≤0.12	0.25	0.5	1	2	4	8	16	32	64	128	≥256
ACHN-490												
KPC (12)	1	5	6									
SME-1				1								
IMP (13)	1	9	3									
NDM-1 (17)		1								1	5	10
VIM (5)		3	1	1								
OXA-48 (19)	1	17			1							
ESBL+impermeability (10)	1	8	1									
AmpC+impermeability (5)		3	2									
Amikacin												
KPC (12)					2	2	1		1	2	4	
SME-1					1							
IMP (13)					2	1	4	3	3			
NDM-1 (17)										1		16
VIM (5)				1	2				1	1		
OXA-48 (19)				6	6	6	1					
ESBL+impermeability (10)					6	1	2		1			
AmpC+impermeability (5)				1	4							
Gentamicin												
KPC (12)		1	5	1	3	1			1			
SME-1				1								
IMP (13)						2	1	4	1	3	2	
NDM-1 (17)										1		16
VIM (5)				2	2						1	
OXA-48 (19)		2	11			1			1	1	3	
ESBL+impermeability (10)			3	3							1	3
AmpC+impermeability (5)			5									

Livermore et al. JAC 2011, Walkty et al. AAC 2014, Landman et al. JAC 2011

Plazomicin

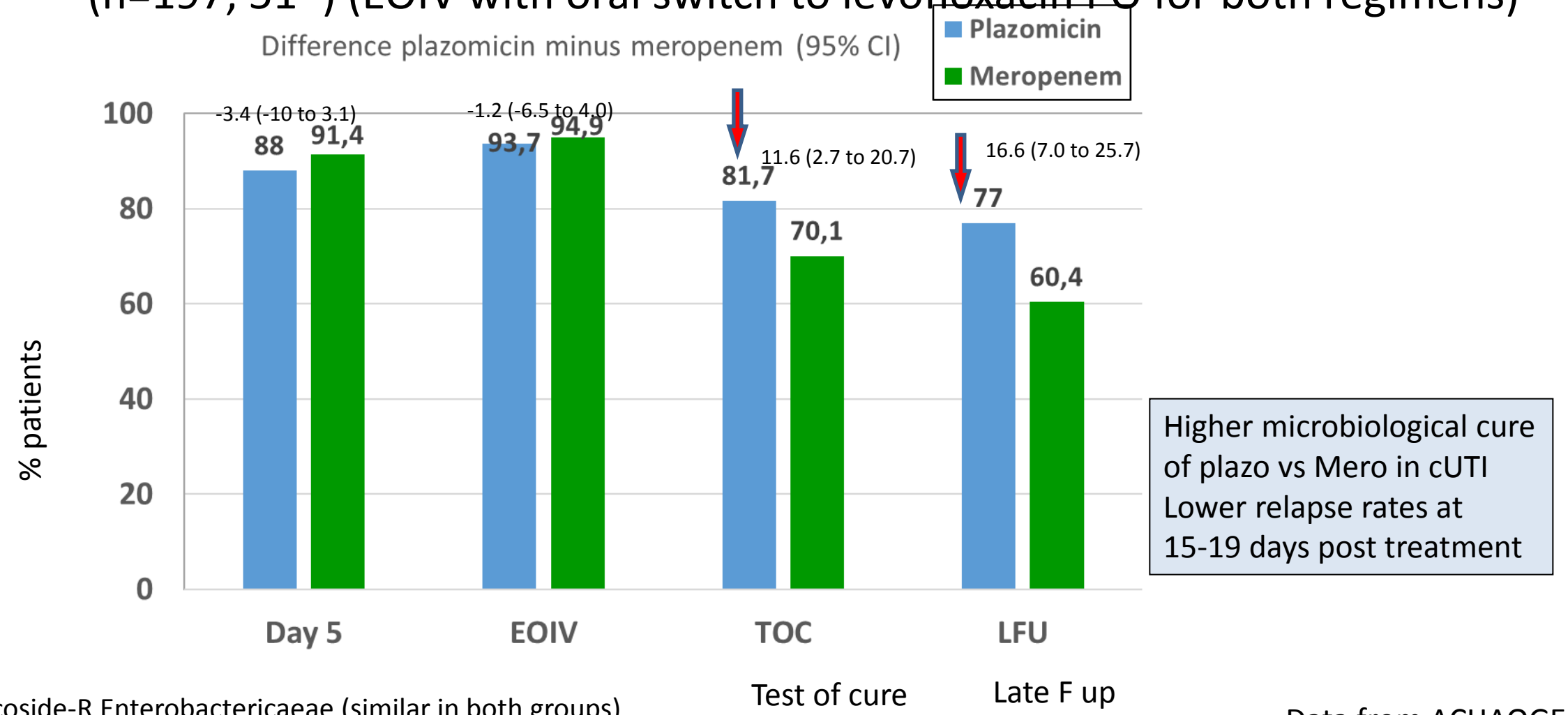
- Dosage: 15 mg/kg/once daily (30 min inf)
- Half-live: 4 hrs
- renal excretion 87%
- less nephrotoxicity, cochleovestibular than other current AGs
- Phase III in cUTI, severe CRE infection



1 Hydroxy-aminobutyrate (HAB), 6' hydroxyethyl sisomicin (gentamicin B family)

Plazomicin - Clinical studies phase 3

- **<u>EPIC study</u>:** cUTI and acute PN: plazomicin (n=191; 52*) > Meropenem (n=197; 51*) (EOIV with oral switch to levofloxacin PO for both regimens)



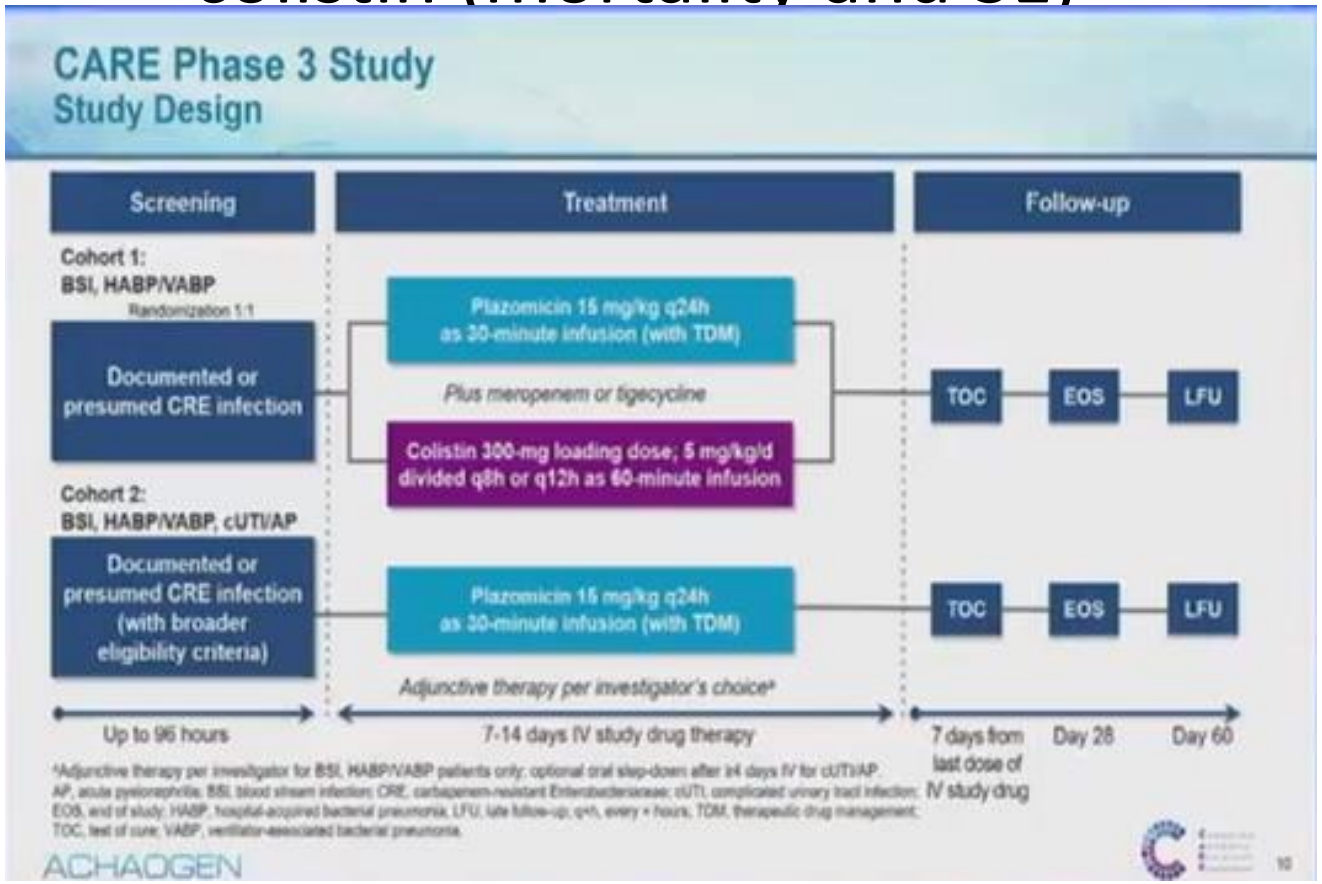
Higher microbiological cure of plazo vs Mero in cUTI
Lower relapse rates at 15-19 days post treatment

* N° aminoglycoside-R Enterobactericaeae (similar in both groups)

Data from ACHAOGEN

Plazomicin - Clinical studies phase 3

- **<u>Care study</u>:** severe infections caused by CRE plazomicin > colistin (mortality and SE)



More rapid clearance of bacteremia and lower mortality rate vs colistine (-60%) at day 60

Colistin posology for CRE sepsis (300 mg loading dose (4 MUI) and 5mg/kg/day per q8h or q12h)
Clinical benefit of combination therapy with Cefta/Avibactam (decreased emergence of resistance ?)

Plazomicin: safety results – drug related AEs

IV study Drug related AEs (Safety Population)	(Cohort 1) Plazomicin (N=18) n(%)	(Cohort 1) Colistin (N=21) n(%)	(Cohort 2) Plazomicin (N=30) n(%)
Anemia	1 (5.6)	0	0
Oral hypoesthesia	0	1 (4.8)	0
Vomiting	1 (5.6)	1 (4.8)	0
Gait disturbance	0	1 (4.8)	0
Systemic candida	1 (5.6)	0	0
Paerethesia	0	1 (4.8)	0
Liver function increased	0	0	1 (3.3)
Renal function events (pooled)[a]	3 (16.7)	8 (38.1)	4 (13.3)

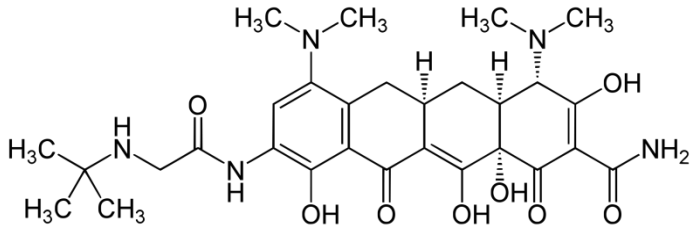
[a] Blood creatinine increased, acute kidney injury, renal failure and renal impairment

Plazomicin Phase 3 efficacy / safety

- **Efficacy benefit for plazomicin in Phase 3 studies** vs standard of care comparator
- **Higher microbiological eradication rates in cUTI** vs meropenem associated with **lower clinical relapse rates**
- **Survival benefit in plazomicin-treated patients** (with CRE infections) sustained through day 60 (associated with more rapid clearance of bacteremia)
- **Safety profile similar to meropenem** (cUTI patients) and more favorable safety profile vs colistin in patients with CRE systemic infections (decreased renal events)

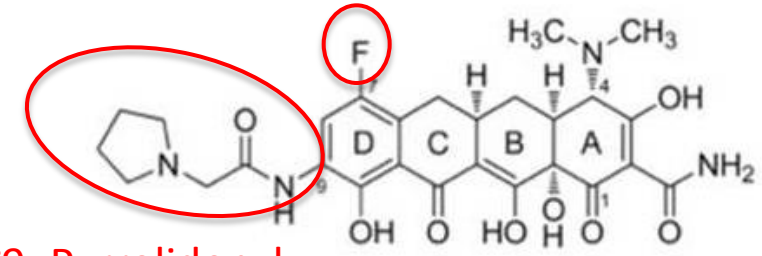
Eravacycline: a novel cycline with broad spectrum encompassing MDR gram-negative

- Structure close to tigecycline
- binding to 30S ribosome (Inhibition of protein synthesis (bacteriostatic)
- Evades most resistant mechanisms of other tetracyclines (tetracycline active efflux pumps, ribosomal protection proteins)



tigecycline

C7: Fluor



C9: Pyrrolidonyl acetamide

eravacycline

- Spectrum: Gram+, Gram- (CRE (class A, B, D), Acinetobacter spp.), anaerobes
- **Dosing IV and oral route** (28% bioavailability)
- **Administration: 1 x/d** (elimination half-life=48h)
- Volume of distribution: 4,2 L/kg
- Biliary excretion (70%), Renal excretion: 15%
- No dosis adjustment if moderate renal/liver failure)

MIC50/MIC90 of *E.coli, K. pneumoniae* (ESBL): 0.25/0.5 µg/ml)
2-8x more active than tigecycline against CRE, and *A. baumannii*
(No activity against *P. aeruginosa, Burkholderia* spp)

Eravacycline – Clinical studies (Phase 3 trials)

- **cIAI** (n=541 pts), Eravacycline (ERA; 1mg/kg/q12h) Vs. Ertapenem (ETP; 1g/q24h), for 4-14 days
  - Exclusion of patients with severe sepsis (mean APACHE II score <7)
  - Low proportion of MDR isolates (<10% in both arms)
  - High rate of clinical cure: ERA: 87% vs ETP: 88%

- **cUTI** (n=908 pts), ERA IV/PO vs ETP/(levofloxacin orally) clinical cure/microbiological response after 6-8days Tx)
  - non-inferiority not achieved at primary end point (oral ERA < LEVO)
  - Role of ERA as first line treatment ? (oral form -> return to phase 2)

Conclusions

- **Several promising new drugs** (new BLI-BL combinations, aminoglycosides, cate cephalosporins)
- **Superiority to current regimens for CRE infection not completely assesed** (Need for RCT, trials in settings other than cIAI, cUTI (e.g. BSI and VAP, MDR infections),
- **Few options for MBLs and for non fermenters** (Acinetobacter spp.)
- **Lack of agents active by oral route**
- **Few options for resistance mechanisms other than beta-lactamases** (porin/efflux)
- **High costs (**may limit access to new agents in resource-poor-settings)
- **Longevity ?** (Early report of resistance to CZA after clinical use)

Careful microbiological monitoring for development and spread of resistance to new agents (appropriate stewardship practice, development of rapid diagnostic techniques allowing targeted therapies)

Acknowledgements

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