NEUE PENEM/BLI-KOMBINATIONEN

F L O R I A N T H A L H A M M E R
KLINISCHE ABTEILUNG FÜR INFEKTIONEN UND TROPENMEDIZIN
UNIVERSITÄTSKLINIK FÜR INNERE MEDIZIN – MEDIZINISCHE UNIVERSITÄT WIEN
www.antibiotika-app.eu – florian.thalhammer@meduniwien.ac.at

www.pbs.org/newshour/health/superbug-appears-spreading-stealthily-u-s-hospitals-study-finds 29.08.2018 09:50

HINWEIS

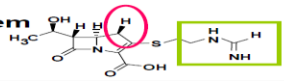
Wertes Auditorium,

die medizinisch-wissenschaftlichen Informationen dieser Präsentation spiegeln ausschließlich meine eigene Meinung und/oder Erfahrung wider.

Der vollständige Einklang der Inhalte mit den jeweiligen Fachinformationen (Austria Codex) kann daher von Seiten des Sponsors (Zulassungsinhabers) dieser Fortbildungsveranstaltung nicht gewährleistet werden.

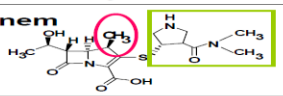
PENEM/BLI KOMBINATIONEN
Doripenem – Imipenem – Meropenem

Imipenem



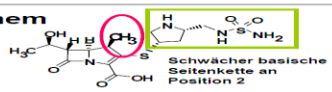
- Instabil gegenüber renaler DHP-I
- Geringere Aktivität gegen gramnegative Erreger

Meropenem

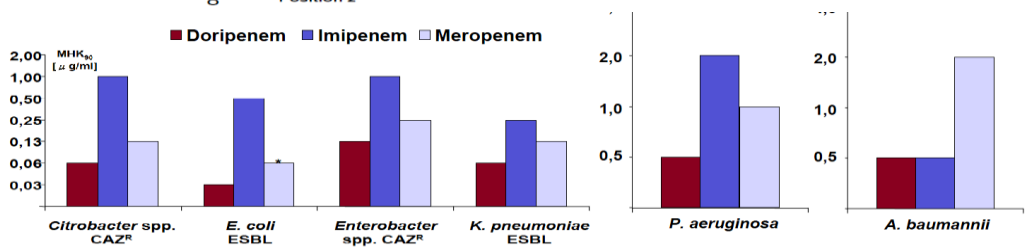


- Stabil gegenüber renaler DHP-I
- Geringeres krampfauslösendes Potential als Imipenem
- Geringere Aktivität gegen grampositive Erreger

Doripenem



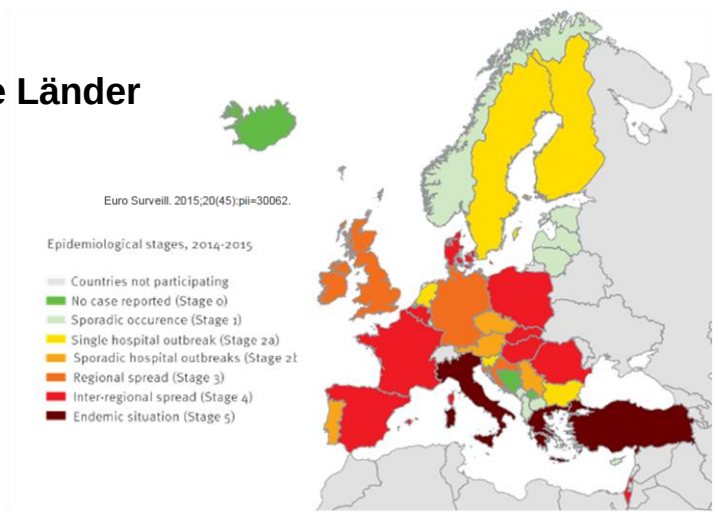
- Stabil gegenüber renaler DHP-I
- Geringeres krampfauslösendes Potential als Imipenem
- Ausgewogenes Aktivitäts-Spektrum



Jones, Antimicrob Agents Chemother 2004

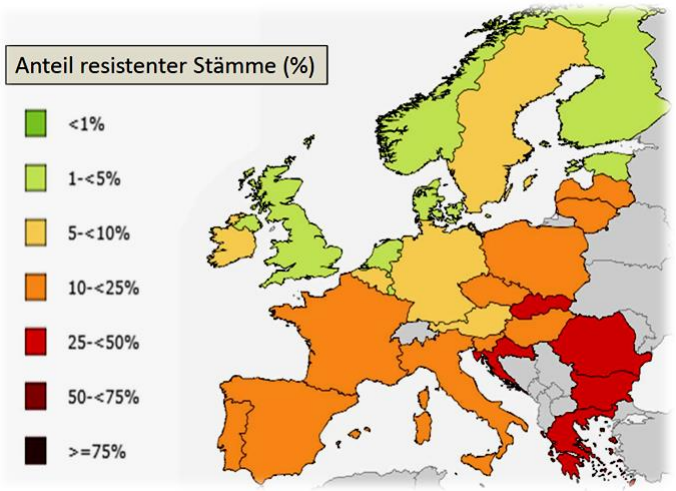
PENEM/BLI KOMBINATIONEN
Carbapenemase-prod Enterobakterien

- 38 europäische Länder
- Mai 2015



Eur Surveill 2015

PENEM/BLI KOMBINATIONEN
MR Pseudomonas aeruginosa



Resistenz
gegen mind 3 AB-Gruppen:

- PiperacillinTazo
- Ciprofloxacin
- Ceftazidim
- Aminoglykosid
- Carbapenem

EARS-Net 2016 – Kresken, PEG Bad Honeff Symposium 2018

PENEM/BLI KOMBINATIONEN
Risikofaktoren für CRE-Akquisitation

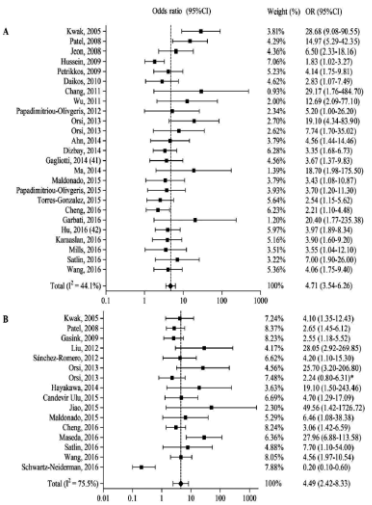
Associated risk factor	Frequency	RE	RE range	No. of cases (range)
Carbapenem use	25	OR	1.83–29.17	9–100
Carbapenem use	1	HR	2.68	19
Cephalosporin use	15	OR	2.24–49.56	15–100
Quinolone use	9	OR	1.18–28.9	18–88
Antibiotic exposure (in general)	9	OR	1.66–13.37	26–464
Other β-lactam use	9	OR	1.08–11.71	34–464
Other	7	OR	1.02–33	25–103
Glycopeptide use	5	OR	2.94–43.84	20–203
No. of antibiotics administered	3	OR	1.6–12.60	59–164
Duration of exposure	3	OR	1.04–9.8	25–104

Loon, Antimicrob Agents Chemother 2018

PENEM/BLI KOMBINATIONEN
Risikofaktoren für CRE-Akquisitation

Associated risk factor	No. of times identified	Pooled OR (95% CI)
Antibiotic exposure		
Carbapenem use	25	4.71 (3.54–6.26)
Cephalosporin use	16	4.49 (2.42–8.33)
Quinolone use	10	2.46 (1.44–4.23)
Other β-lactam use	9	2.00 (1.49–2.70)
Glycopeptide use	5	4.18 (2.30–7.60)
Other risk factors		
Underlying disease or condition	31	2.54 (2.08–3.09)
Invasive procedures	20	4.67 (3.59–6.07)
Medical devices	17	5.09 (3.38–7.67)
ICU admission	15	4.62 (2.46–8.69)
Patient demographic characteristics	13	1.08 (1.03–1.14)
Exposure to hospital care	12	1.05 (1.02–1.08)
Mechanical ventilation	11	1.96 (1.42–2.69)
CRE exposure	5	4.10 (1.46–11.52)

A … Carbapenem
B … Cephalosporin

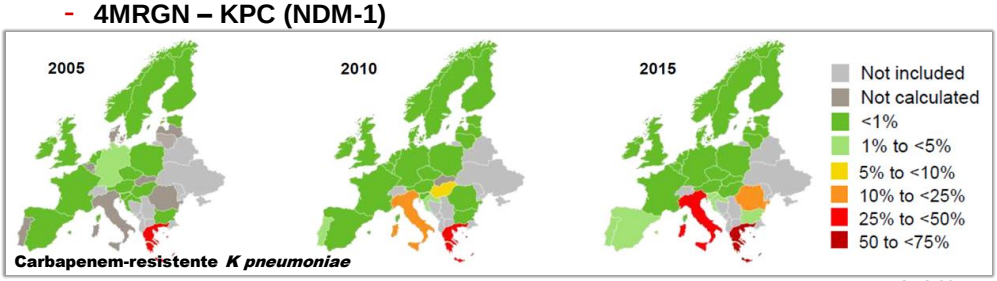


Loon, Antimicrob Agents Chemother 2018

PENEM/BLI KOMBINATIONEN
Unsere Sorgenkinder

GRAM-NEGATIVE ERREGER

- **Escherichia coli**
  - 3MRGN – ESBL
- **Klebsiella pneumoniae**
  - 3MRGN – ESBL
  - 4MRGN – KPC (NDM-1)
- **Acinetobacter baumanii**
  - 4MRGN
- **Pseudomonas aeruginosa**
  - 4MRGN



ECDC 2017

PENEM/BLI KOMBINATIONEN
Piperacillin/Tazobactam

- **Tazobactam**
  - 10-fach aktiver als Clavulansäure gegen TEM
  - in-vitro Aktivität gegen ESBL häufig gegeben
  - Inokulum-Effekt analog zu Cefepim beschrieben
- **Kombination mit Piperacillin**
  - reduziert renale Sekretion > höhere Piperacillinspiegel
  - schützt Piperacillin vor Hydrolyse durch Betalaktamasen
- **Studien mit unterschiedl Ergebnissen**
  - keine prospektiv randomisierten Studien bisher publiziert
  - MERINO-Studie Studienergebnisse
  - kritisch kranke ICU-Patienten deutlich unterrepräsentiert
- **Dosierungsoptimum**
  - Dosis 4 x 4.5 g
  - Bolus, prolongiert, kontinuierlich


Arguments in favour
- By definition, ß-lder class A ESBL producers are inhibited by antimicrobials that inactivate ß-lactamases such as clavulanate or tazobactam
- Emerging data from some large cohort studies and a meta-analysis support the safety and efficacy of BLI/BLIs
- Drugs used regularly against Enterobacteriaceae expressing class A ß-lactamases (eg, TEM-1 in ampicillin-resistant Escherichia coli, SHV-1 in klebsiella pneumoniae), and other ß-lactamase-producing species (eg, Haemophilus influenzae, Staphylococcus aureus) without strong evidence for frequent clinical failure
- ESBL producers are frequently susceptible in vitro to piperacillin-tazobactam (especially ESBL-producing E coli) in many parts of the world
- Carbapenems should be reserved for specific situations in which no other drugs are available
- Few clinical studies clearly show inferiority of BLIBs when compared with carbapenems in the treatment of susceptible ESBL producers
- Possible decreased selection pressure for carbapenem-resistant strains or Clostridium difficile might be more ecologically benign in some situations compared with third-generation cephalosporins, carbapenems, or quinolones


Arguments against
- Carbapenems remain stable to ESBLs and are recommended as first-line therapy for serious infections
- Scarce published clinical experience on the efficacy of BLIBs against ESBL producers causing infections outside the urinary tract
- An inoculum effect shown in mouse models, which might limit efficacy
- Increasing resistance to BLIBs in ESBL producers, especially K pneumoniae, thus limiting efficacy in empirical therapy
- Overexpression of ß-lactamases (including by other non-ESBLs) that might overwhelm the inhibitor component
- No head-to-head randomised trials to assess BLIBs in comparison with carbapenems
- Poor drug concentration attainment with standard doses of piperacillin-tazobactam for isolates with high minimum inhibitory concentrations but still within the Clinical Laboratory Standards Institute susceptible range (eg, 8–16 mg/L)
- Complex co-resistance mechanisms, including other enzymes not well inhibited by tazobactam or clavulanate (eg, plasmid-derived AmpC, or development of inhibitor-resistant enzymes

Komuro, JAC 1994 – Bonfiglio, Duagn Microbiol Infect Dis 1994 – Bonomo, FEMS Microbiol Lett 1997 – Lister, AAC 1999
Thomson, AAC 2001– Shlaes, Ann N Y Acad Sci 2013 – Harris, Lancet Infect Dis 2015 – Ruppé, Ann Intensive Care 2015

PENEM/BLI KOMBINATIONEN
Carbapenem sparende Thrapie

MERINO STUDIE

Harris, JAMA 2018

PENEM/BLI KOMBINATIONEN
Carbapenem sparende Thrapie

OBJECTIVES To determine whether definitive therapy with piperacillin-tazobactam is noninferior to meropenem (a carbapenem) in patients with bloodstream infection caused by ceftriaxone-nonsusceptible *E coli* or *K pneumoniae*.

DESIGN, SETTING, AND PARTICIPANTS Noninferiority, parallel group, randomized clinical trial included hospitalized patients enrolled from 26 sites in 9 countries from February 2014 to July 2017. Adult patients were eligible if they had at least 1 positive blood culture with *E coli* or *Klebsiella* spp testing nonsusceptible to ceftriaxone but susceptible to piperacillin-tazobactam. Of 1646 patients screened, 391 were included in the study.

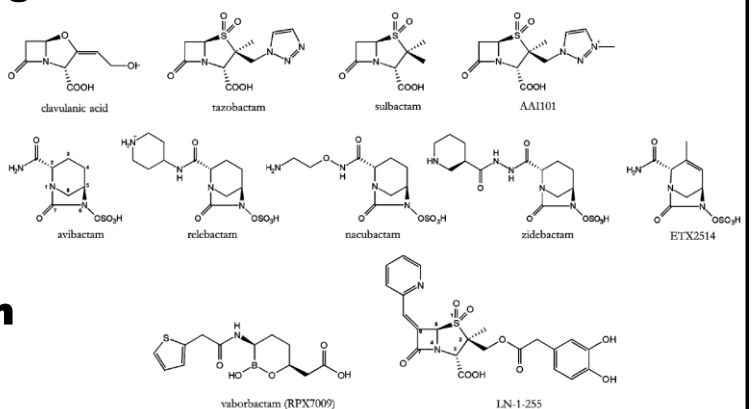
INTERVENTIONS Patients were randomly assigned 1:1 to intravenous piperacillin-tazobactam, 4.5 g, every 6 hours (n = 188 participants) or meropenem, 1 g, every 8 hours (n = 191 participants) for a minimum of 4 days, up to a maximum of 14 days, with the total duration determined by the treating clinician.

MAIN OUTCOMES AND MEASURES The primary outcome was all-cause mortality at 30 days after randomization. A noninferiority margin of 5% was used.

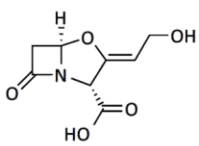
Harris, JAMA 2018

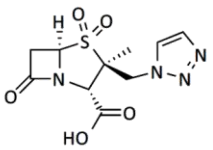
PENEM/BLI KOMBINATIONEN
Betalaktamasehemmer

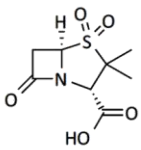
- **Avibactam**
- **Clavulansäure**
- **ETX514**
- **Nacubactam**
- **Relebactam**
- **Sulbactam**
- **Tazobactam**
- **Vaborbactam**
- **Zidebactam**

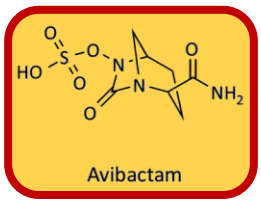


PENEM/BLI KOMBINATIONEN
Avibactam bis Vaborbactam

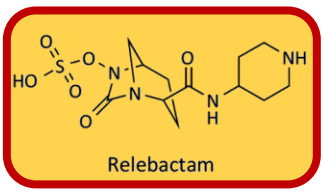

Clavulanic Acid

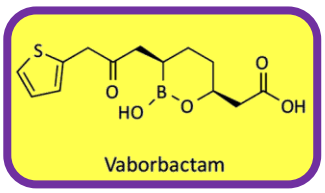

Tazobactam

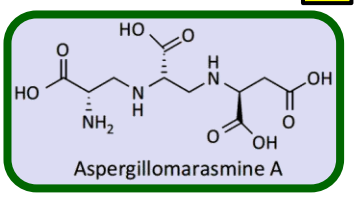

Sulbactam


Avibactam

Klasse I.A


Relebactam


Vaborbactam

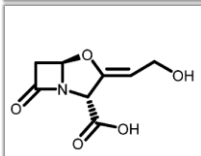

Aspergillomarasmine A

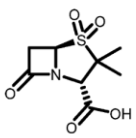
Diazabizyklooktan (DABCO): Kombination mit Ceftazidim bzw. Imipenem
Boronsäure: Kombination mit Meropenem
Metallobetalaktamaseinhibitor

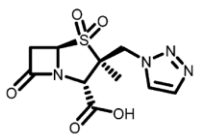
Wright, Trends Microbiol 2016

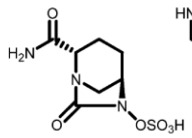
PENEM/BLI KOMBINATIONEN
Avibactam & Relebactam

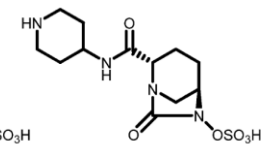
		Clavulansäure	Tazobactam	Avibactam
Class A	TEM, SHV	✓	✓	✓
	CTX-M	✗	✓	✓
	PER, VEB, GES	✗	✓	✓
	KPC	✗	✗	✓
Class B	IMP, VIM, NDM1	✗	✗	✗
Class C	chromosomal Enterobacteriaceae AmpC	✗	✗	✓
	chromosomal Pseudomonas AmpC	✗	✗	✓
	Plasmid-encoded ACC, DHA, CMY, FOX, LAT, MOX, MIR, ACT	✗	✗	✓
Class D	OXA-1, -31, -10, -13	variabel OXA-1, -10	variabel	variabel OXA-1, -31
	Carbapenemasetyp OXA-23, -40, -48, -58	variabel	variabel OXA-23, -48	variabel OXA-48


clavulanic acid


sulbactam


tazobactam


avibactam


relebactam

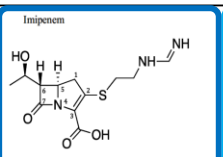
Lagacé-Wiens, Core Evid 2014 – Hecker, J Med Chem 2015 – Wright, Trends Microbiol 2016

PENEM/BLI KOMBINATIONEN
BLI im Aktivitätsvergleich

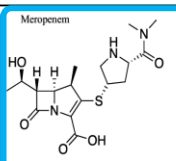
β-lactamase inhibitor

	Relebactam	Vaborbactam	Avibactam
Class A			
TEM	+	+	+
SHV	+	+	+
CTX-M	+	+	+
KPC	+	+	+
Class B			
MBL	–	–	–
Class C			
AmpC	+	+	+
Class D			
OXA	±	–	±

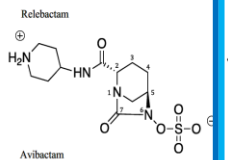
Imipenem



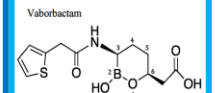
Meropenem



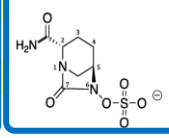
Relebactam



Vaborbactam

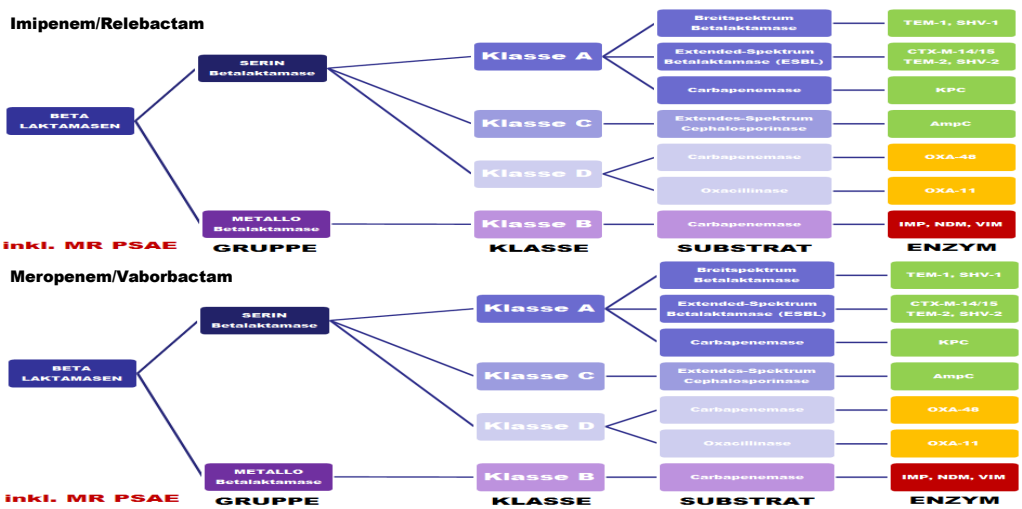


Avibactam

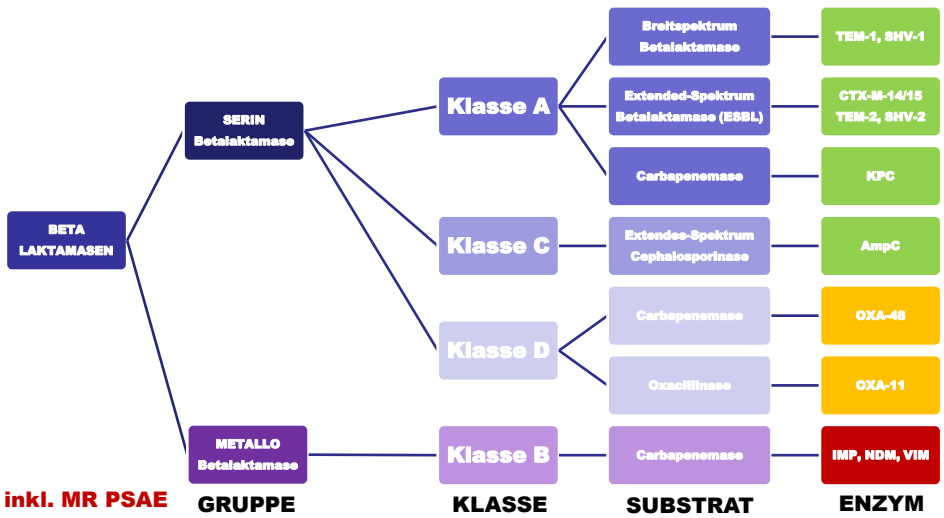


Zhanel, Drugs 2018

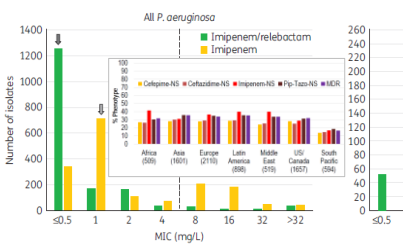
PENEM/BLI KOMBINATIONEN
Die zwei Neuankömmlinge

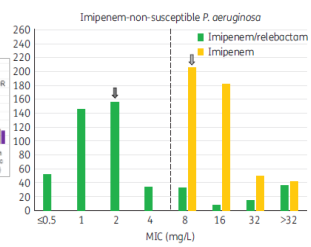


PENEM/BLI KOMBINATIONEN
Imipenem/Relebactam

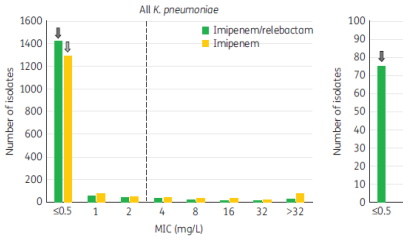


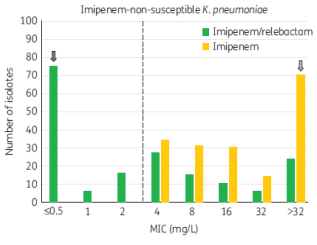
PENEM/BLI KOMBINATIONEN
Imipenem/Relebactam – SMART-Studie





	No. of isolates (% of phenotype)	
Phenotype/β-lactamase content	*P. aeruginosa* (*N* = 477)	*K. pneumoniae* (*N* = 179)
Imipenem/relebactam-susceptible (*n*)	387	97
KPC		47 (48.5)
KPC + ESBL		27 (27.8)
KPC + AmpC		4 (4.1)
KPC + ESBL + AmpC		1 (1.0)
KPC + OXA-48 + ESBL		1 (1.0)
OXA-48		1 (1.0)
OXA-48 + ESBL		16 (16.5)
ESBL	24 (6.2)	
AmpC	4 (1.0)	
no acquired β-lactamase detected	359 (92.8)	
Imipenem/relebactam-non-susceptible (*n*)	90	82
MBL	52 (57.8)	4 (4.9)
MBL + ESBL	1 (1.1)	30 (36.6)
MBL + ESBL + AmpC		3 (3.7)
MBL + OXA-48		
MBL + OXA-48 + ESBL		4 (4.9)
OXA-48 + ESBL		34 (41.5)
OXA-48 + AmpC		1 (1.2)
OXA-48 + ESBL + AmpC		6 (7.3)
GES carbapenemase	19 (21.1)	
ESBL	2 (2.2)	
AmpC	1 (1.1)	
no acquired β-lactamase detected	15 (16.7)	





Lob, ECCMID 2018 – Karlowsky, J Antimicrob Chemother 2018

PENEM/BLI KOMBINATIONEN
Imipenem/Relebactam

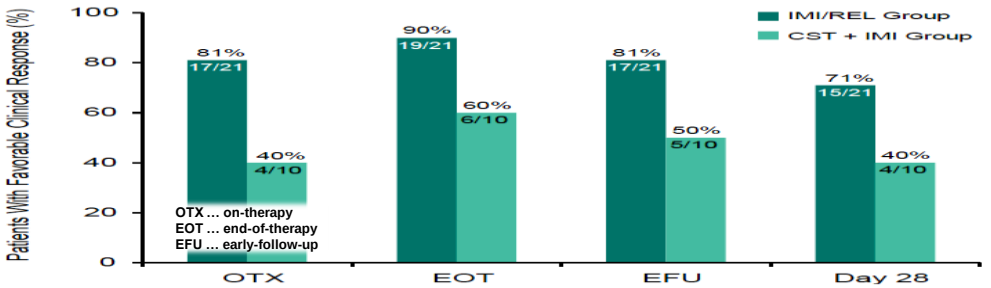
organism	strain	enzyme	biapenem		meropenem		ertapenem		imipenem	
			alone	with 9f	alone	with 9f	alone	with 9f	alone	with 9f
Escherichia coli	EC1007	KPC-3	8	≤0.06	4	≤0.06	8	≤0.06	8	0.13
Enterobacter cloacae	ECL1058	KPC-3, SHV-11, TEM-1	8	≤0.06	8	≤0.06	32	0.25	8	0.25
Klebsiella oxytoca	KX1019	KPC-2, OXA-2	8	0.25	4	≤0.06	16	0.25	4	0.13
Klebsiella oxytoca	KX1017	KPC-2, OXA-2, SHV-30	4	≤0.06	4	≤0.06	16	0.25	8	0.13
Klebsiella pneumoniae	KP1004	KPC-2, TEM-1, SHV-11	8	≤0.06	8	≤0.06	32	≤0.06	8	≤0.06
Klebsiella pneumoniae	KP1008	KPC-2	8	≤0.06	4	≤0.06	8	≤0.06	4	≤0.06
Klebsiella pneumoniae	KP1082	KPC-2, SHV-1	4	≤0.06	4	≤0.06	4	≤0.06	4	0.13
Klebsiella pneumoniae	KP1087	KPC-2, CTX-M-15, SHV-11, TEM-1	16	0.25	64	1	>64	2	16	0.25
Klebsiella pneumoniae	KP1083	KPC-3, SHV-1, TEM-1	16	≤0.06	16	≤0.06	32	≤0.06	16	0.13
Klebsiella pneumoniae	KP1084	KPC-3, SHV-11, TEM-1	64	0.25	>64	0.5	>64	4	64	0.25
Klebsiella pneumoniae	KP1088	KPC-3, SHV-11, TEM-1	32	≤0.06	8	≤0.06	16	≤0.06	32	≤0.06

enzyme	class	9f	clavulanic acid	tazobactam
KPC-2	A	0.069	41.2	1.6
CTX-M-15	A	0.044	0.027	0.001
SHV-12	A	0.029	≤0.039	0.0004
TEM-10	A	0.110	0.020	0.005
P99	C	0.053	1106	1.10
CMY-2	C	0.099	845	0.71

Hecker, J Med Chem 2015

PENEM/BLI KOMBINATIONEN
Imipenem/Relebactam

Endpoint	IMI/REL (N=21)		CST + IMI (N=10)		Unadjusted Difference	Adjusted Difference[b]	
	n	%	n	%	%	%	(90% CI)
Favorable overall response	15	71.4%	7	70.0%	1.4%	-7.3%	(-27.5, 21.4)
HABP/VABP	7/8	87.5%	2/3	66.7%	20.8		
cIAI	0/2	0.0%	0/2	0.0%	0.0		
cUTI	8/11	72.7%	5/5	100.0%	-27.3 (-52.8, 12.8)		
Favorable clinical response (Day 28)	15	71.4%	4	40.0%	31.4%	26.3%	(1.3, 51.5)
28-day all-cause mortality	2	9.5%	3	30.0%	-20.5%	-17.3%	(-46.4, 6.7)



Motsch, ECCMID 2018

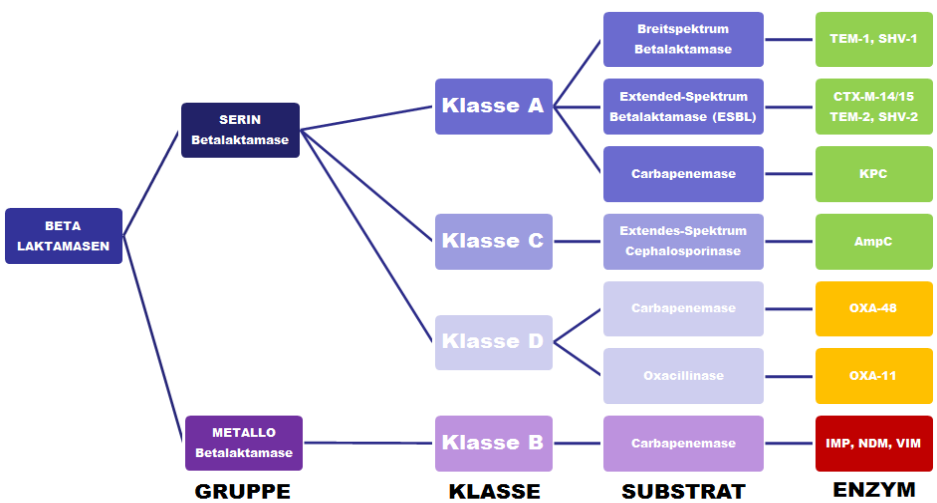
PENEM/BLI KOMBINATIONEN
Imipenem/Relebactam in der Lunge

Analyte	Matrix	$AUC_{0-\infty}$ ($\mu M \cdot h$)	AUC_{0-3} ($\mu M \cdot h$)	C_{max} (μM)	T_{max} (h)	$t_{1/2}$ (hr)	ELF/plasma $AUC_{0-\infty}$ ratio	Adjusted ELF/plasma $AUC_{0-\infty}$ ratio
Relebactam							43.0	53.7
	Plasma	81.2	64.7	47.9	0.50	1.24		
	ELF	34.9	26.7	15.3	0.50	1.29		
	AC	23.6	12.8	7.81	1.00	2.25		
Imipenem							44.2	55.2
	Plasma	130	114	99.6	0.50	0.95		
	ELF	57.4	48.4	32.6	0.50	1.03		
	AC	—	—	—	—	—		

	Relebactam concn in ELF (μM)		Imipenem concn in ELF (μM)		Relebactam/imipenem concn ratio	
Time (h)	GM	95% CI	GM	95% CI	GMR	90% CI
0.5	14.93	9.89, 22.53	32.09	21.26, 48.44	0.47	0.45, 0.49
1	10.93	7.24, 16.50	20.27	13.43, 30.59	0.54	0.52, 0.56
1.5	9.49	6.29, 14.32	16.47	10.92, 24.87	0.58	0.55, 0.60
3	4.27	2.83, 6.45	5.99	3.97, 9.04	0.71	0.68, 0.74

Rizk, Antimicrob Agents Chemother 2018

PENEM/BLI KOMBINATIONEN
Meropenem/Vaborbactam



PENEM/BLI KOMBINATIONEN
Meropenem/Vaborbactam

- Betalaktamaseinhibitor
  - RPX7009
- wirkungsvolle Serinproteaseinhibitoren
- Bildung reversibler kovalenten Bindung zwischen Serin und Boronsäuregruppe
- cyclische Boronsäureester als Inhibitoren
- Kombination mit Meropenem

Compound	Activity	All 2,029 isolates	*E. coli* ESBL (27)	*K. pneumoniae* ESBL (71)	*K. pneumoniae* KPC (26)
GSK2251052	Range (µg/mL)	0.25–4	0.5–2	0.5–2	0.25–2
	MIC_{50} (µg/mL)	1	1	1	2
	% Susceptible	-	-	-	-
Levofloxacin	Range (µg/mL)	≤0.5->16	≤0.5->16	≤0.5->16	≤0.5->16
	MIC_{90} (µg/mL)	16	>16	>16	>16
	% Susceptible	81.4	3.7	28.2	15.4
Gentamicin	Range (µg/mL)	≤0.5->16	≤0.5->16	≤0.5->16	≤0.5->16
	MIC_{90} (µg/mL)	>16	>16	>16	16
	% Susceptible	87.2	63.0	43.7	76.9
Tigecycline	Range (µg/mL)	0.06-8	0.12-1	0.12-4	0.25-4
	MIC_{90} (µg/mL)	2	0.5	2	2
	% Susceptible	92.2	100	95.8	92.3
Polymyxin B	Range (µg/mL)	≤0.25->8	0.5-4	0.5->8	0.5->8
	MIC_{90} (µg/mL)	>8	2	2	>8
	% Susceptible	58.7	96.3	93.0	88.5
Imipenem	Range (µg/mL)	≤0.03 ->64	0.12-16	0.06-1	8->64
	MIC_{90} (µg/mL)	2	0.5	0.5	64
	% Susceptible	73.5	96.3	100	0

MIC_{90}: Susceptible; Intermediate; Resistant (CLSI Breakpoints M100-S21 & FDA)

P. Aeruginosa (n-98)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	Range (µg/ml)	% Susceptible
Piperacillin-tazobactam	16/4	>128/4	16/4 to > 128/4	52
Ceftazidime	8	>16	1 to > 16	37
Amikacin	4	16	≤0.5 to > 64	94
Ciprofloxacin	>4	>4	≤0.125 to > 4	35
Meropenem	8	32	4 to >64	0
Meropenem-RPX7009 (4µg/ml)	8/4	32/4	0.125/4 to >64/4	NA
Meropenem-RPX7009 (8µg/ml)	8/8	32/8	0.25/8 to 64/8	NA

Stintzi, PNAS 2000 – Mendes, ICAAC 2010 – Page, Ann NY Acad Sci 2013 – Lapuebla, Antimicrob Agents Chemother 2015
Chellat, Angew Chemie 2016

PENEM/BLI KOMBINATIONEN
Meropenem/Vaborbactam

Organism group (no. of isolates tested) and antimicrobial agent	No. of isolates (cumulative %) from all regions at meropenem-vaborbactam MIC (µg/ml) of: ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32	$MIC_{50/90}$ (µg/ml) by region, with no. (%) of isolates for each organism group[a] Overall	Asia-Pacific	Europe	Latin America	United States
CRE (265)														265 (2.5)	9 (1.5)	167 (3.2)	24 (4.8)	65 (1.6)
Meropenem-vaborbactam	36 (13.6)	20 (21.1)	7 (23.8)	21 (31.7)	29 (42.6)	34 (55.5)	26 (65.3)	15 (70.9)	23 (79.6)	12 (84.2)	8 (87.2)	14 (92.5)	20 (100.0)	0.5/32	32/NA	1/32	0.12/4	0.03/1
Meropenem					1 (0.4)	1 (0.8)	3 (1.9)	16 (7.9)	48 (26.0)	37 (40.0)	34 (52.8)	29 (63.8)	96 (100.0)	16/>32	>32/NA	16/>32	32/>32	16/>32
Carbapenem-resistant *K. pneumoniae* (211)														211 (10.5)	9 (4.5)	132 (13.8)	24 (15.4)	46 (6.6)
Meropenem-vaborbactam	29 (13.7)	17 (21.8)	6 (24.6)	20 (34.1)	28 (47.4)	27 (60.2)	21 (70.1)	8 (73.9)	11 (79.1)	6 (82.0)	7 (85.3)	12 (91.0)	19 (100.0)	0.5/32	32/NA	0.5/>32	0.12/4	0.03/1
Meropenem								8 (3.8)	28 (17.1)	27 (29.9)	28 (43.1)	26 (55.5)	94 (100.0)	32/>32	>32/NA	32/>32	32/>32	16/>32
KPC producers (135)														135 (1.3)	0 (0)	63 (1.2)	21 (4.2)	51 (1.2)
Meropenem-vaborbactam	35 (25.9)	19 (40.0)	7 (45.2)	19 (59.3)	24 (77.0)	19 (91.1)	7 (96.3)	3 (98.5)	1 (99.3)	1 (100.0)				0.12/0.5	NA	0.25/0.5	0.12/2	0.03/0.5
Meropenem							1 (0.7)	6 (5.2)	11 (13.3)	10 (20.7)	21 (36.3)	16 (48.1)	70 (100.0)	>32/>32	NA	>32/>32	>32/>32	16/>32
OXA-48-like-producers (25)														25 (0.2)	0 (0)	23 (0.4)	1 (0.2)	1 (<0.1)
Meropenem-vaborbactam						2 (8.0)	0 (8.0)	0 (8.0)	3 (20.0)	5 (40.0)	5 (60.0)	5 (80.0)	5 (100.0)	16/>32	NA	16/>32	8[b]	0.5[b]
Meropenem						1 (4.0)	0 (4.0)	1 (8.0)	2 (16.0)	5 (36.0)	5 (56.0)	6 (80.0)	5 (100.0)	16/>32	NA	16/>32	8[b]	2[b]
MBL producers (41)														41 (0.4)	7 (1.2)	32 (0.6)	1 (0.2)	1 (<0.1)
Meropenem-vaborbactam							2 (4.9)	4 (14.6)	5 (26.8)	5 (39.0)	2 (43.9)	8 (63.4)	15 (100.0)	32/>32	32/NA	32/>32	4[b]	>32[b]
Meropenem							1 (2.4)	5 (14.6)	6 (29.3)	4 (39.0)	2 (43.9)	5 (56.1)	18 (100.0)	32/>32	>32/NA	16/>32	2[b]	>32[b]
Carbapenemase-negative isolates (63)														63 (0.6)	2 (0.3)	48 (0.9)	1 (0.2)	12 (0.3)
Meropenem-vaborbactam	1 (1.6)	1 (3.2)	0 (3.2)	2 (6.3)	5 (14.3)	13 (34.9)	17 (61.9)	7 (73.0)	14 (95.2)	1 (96.8)	1 (98.4)	1 (100.0)		1/4	16/NA	1/4	1[b]	0.5/4
Meropenem					1 (1.6)	0 (1.6)	1 (3.2)	3 (7.9)	29 (54.0)	18 (82.5)	6 (92.1)	2 (95.2)	3 (100.0)	4/16	8/NA	4/16	8[b]	4/32
MDR isolates (1,210)														1,210 (11.6)	65 (11.1)	714 (13.7)	116 (23.4)	315 (7.6)
Meropenem-vaborbactam	499 (41.2)	295 (65.6)	106 (74.4)	65 (79.8)	59 (84.6)	54 (89.1)	40 (92.4)	16 (93.7)	22 (95.5)	12 (96.5)	8 (97.2)	14 (98.3)	20 (100.0)	0.03/1	≤0.015/16	0.03/1	0.03/0.5	0.03/0.12
Meropenem	214 (17.7)	312 (43.5)	229 (62.4)	83 (69.3)	30 (71.7)	35 (74.6)	37 (77.7)	30 (80.2)	46 (84.0)	36 (86.9)	34 (89.8)	28 (92.1)	96 (100.0)	0.06/32	0.03/32	0.06/32	0.03/>32	0.06/16
XDR isolates (161)														161 (1.5)	9 (1.5)	94 (1.8)	22 (4.4)	36 (0.9)
Meropenem-vaborbactam	19 (11.8)	18 (23.0)	9 (28.6)	10 (34.8)	15 (44.1)	17 (54.7)	23 (68.9)	9 (74.5)	6 (78.3)	6 (82.0)	5 (85.1)	10 (91.3)	14 (100.0)	0.5/32	32/NA	1/>32	0.12/2	0.03/0.5
Meropenem	1 (0.6)	4 (3.1)	5 (6.2)	6 (9.9)	2 (11.2)	2 (12.4)	1 (13.0)	11 (19.9)	24 (34.8)	22 (48.4)	18 (59.6)	15 (68.9)	50 (100.0)	16/>32	>32/NA	8/>32	32/>32	16/>32

Castanheira, Antimicrob Agents Chemother 2017

PENEM/BLI KOMBINATIONEN
Meropenem/Vaborbactam

			Antibiotic MIC (μg/ml) in the absence or presence of BLIs									
Strain	Beta-lactamase	Class	CAZ	CAZ + VAB	CAZ + TZB	CAZ + CLA	ATM	ATM + VAB	ATM + TZB	ATM + CLA	MEM	MEM + VAB
ECM6704	None		≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	≤0.03	≤0.03
ECM6701	KPC-2	A-CARB	4	≤0.125	4	2	32	≤0.125	16	16	2	≤0.03
ECM6702	KPC-3	A-CARB	16	≤0.125	16	8	32	≤0.125	16	16	2	≤0.03
ECM6706	SME-2	A-CARB	1	≤0.125	≤0.125	0.25	>128	0.25	4	16	16	≤0.03
ECM6696	NMC-A	A-CARB	0.5	≤0.125	0.25	0.25	64	≤0.125	8	8	1	≤0.03
ECM6718	SHV-5	A-ESBL	8	0.5	≤0.125	≤0.125	16	1	≤0.125	≤0.125	≤0.03	≤0.03
ECM6698	SHV-12	A-ESBL	32	2	≤0.125	≤0.125	32	4	≤0.125	≤0.125	≤0.03	≤0.03
ECM6699	SHV-18	A-ESBL	8	0.5	≤0.125	≤0.125	16	1	≤0.125	≤0.125	≤0.03	≤0.03
ECM6713	TEM-10	A-ESBL	128	16	0.25	0.25	16	4	≤0.125	≤0.125	≤0.03	≤0.03
ECM6714	TEM-26	A-ESBL	128	2	≤0.125	0.25	8	2	≤0.125	≤0.125	≤0.03	≤0.03
ECM6695	CTX-M-3	A-ESBL	1	≤0.125	≤0.125	≤0.125	4	≤0.125	≤0.125	≤0.125	≤0.03	≤0.03
ECM6693	CTX-M-14	A-ESBL	1	≤0.125	≤0.125	≤0.125	4	≤0.125	≤0.125	≤0.125	≤0.03	≤0.03
ECM6694	CTX-M-15	A-ESBL	4	≤0.125	≤0.125	≤0.125	8	0.25	≤0.125	≤0.125	≤0.03	≤0.03
ECM6692	DHA-1	C	8	0.25	≤0.125	8	2	0.25	≤0.125	2	≤0.03	≤0.03
ECM6691	MIR-1	C	32	0.5	8	32	32	1	16	32	≤0.03	≤0.03
ECM6705	FOX-5	C	32	8	32	32	2	0.5	2	2	≤0.03	≤0.03
ECM6715	AmpC-ECL (P99-like)	C	16	0.25	1	16	16	0.5	2	16	≤0.03	≤0.03
ECM6700	CMY-2	C	16	0.25	0.5	16	8	0.25	1	8	≤0.03	≤0.03
ECM6697	OXA-2	D	1	1	0.25	≤0.125	≤0.125	ND	ND	ND	≤0.03	≤0.03
ECM6712	OXA-10	D	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	ND	ND	ND	≤0.03	≤0.03
ECM6716	OXA-48	D-CARB	≤0.125	≤0.125	≤0.125	≤0.125	≤0.125	ND	ND	ND	0.125	0.125
ECM6703	NDM-1	B	>128	>128	>128	>128	≤0.125	≤0.125	≤0.125	≤0.125	16	16
ECM6711	VIM-1	B	128	128	128	128	≤0.125	≤0.125	≤0.125	≤0.125	1	1

[a]All beta-lactamase inhibitors were tested at a fixed concentration of 4 μg/ml. BLIs, beta-lactamase inhibitors; CAZ, ceftazidime; ATM, aztreonam; MEM, meropenem; VAB, vaborbactam; TZB, tazobactam; CLA, clavulanic acid; ND, not done; A-CARB, class A carbapenemase; D-CARB, class D carbapenemase.

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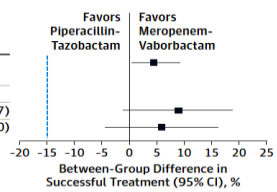
PENEM/BLI KOMBINATIONEN
Meropenem/Vaborbactam – TANGO I

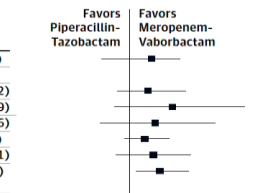
Primary end points

	No. of Patients Successfully Treated/Total No. (%)		Between-Group Difference (95% CI), %
	Meropenem-Vaborbactam	Piperacillin-Tazobactam	
FDA primary: overall success at end of intravenous treatment (microbiologic MITT analysis)[a,b]	189/192 (98.4)	171/182 (94.0)	4.5 (0.7 to 9.1)
EMA primary: microbial eradication at test of cure			
Microbiologic MITT analysis[b]	128/192 (66.7)	105/182 (57.7)	9.0 (-0.9 to 18.7)
Microbiologic evaluable analysis	118/178 (66.3)	102/169 (60.4)	5.9 (-4.2 to 16.0)



Secondary end points

	No. of Patients Successfully Treated/Total No. (%)		Between-Group Difference (95% CI), %
	Meropenem-Vaborbactam	Piperacillin-Tazobactam	
Overall success at test of cure[a]	143/192 (74.5)	128/182 (70.3)	4.1 (-4.9 to 9.1)
Overall success at end of intravenous treatment[a]			
Acute pyelonephritis	117/120 (97.5)	95/101 (94.1)	3.4 (-2.0 to 10.2)
Complicated UTI, removable infection source[c]	35/35 (100)	35/38 (92.1)	7.9 (-2.5 to 20.9)
Complicated UTI, nonremovable infection source	37/37 (100)	41/43 (95.3)	4.7 (-5.1 to 15.6)
Clinical cure at end of intravenous treatment[d]	189/192 (98.4)	174/182 (95.6)	2.8 (-0.7 to 7.1)
Clinical cure at test of cure	174/192 (90.6)	157/182 (86.3)	4.4 (-2.2 to 11.1)
Microbial eradication at end of intravenous treatment (FDA criteria)	188/192 (97.9)	168/182 (92.3)	5.6 (1.4 to 10.7)
Microbial eradication at test of cure (FDA criteria)	132/192 (68.8)	113/182 (62.1)	6.7 (-3.0 to 16.2)



Kaye, JAMA 2018

PENEM/BLI KOMBINATIONEN
Meropenem/Vaborbactam – TANGO I

Adverse Event	No. (%) Meropenem-Vaborbactam (n = 272)	Piperacillin-Tazobactam (n = 273)	Total (n = 545)
Headache	24 (8.8)	12 (4.4)	36 (6.6)
Diarrhea	9 (3.3)	12 (4.4)	21 (3.9)
Nausea	5 (1.8)	4 (1.5)	9 (1.7)
Asymptomatic bacteriuria	4 (1.5)	4 (1.5)	8 (1.5)
Catheter site phlebitis	5 (1.8)	3 (1.1)	8 (1.5)
Infusion site phlebitis	6 (2.2)	2 (0.7)	8 (1.5)
Urinary tract infection	4 (1.5)	4 (1.5)	8 (1.5)
Hypokalemia	3 (1.1)	4 (1.5)	7 (1.3)
Vaginal infection	1 (0.4)	6 (2.2)	7 (1.3)
Alanine aminotransferase increased	5 (1.8)	1 (0.4)	6 (1.1)
Anemia	2 (0.7)	4 (1.5)	6 (1.1)
Aspartate aminotransferase increased	4 (1.5)	2 (0.7)	6 (1.1)
Pyrexia	4 (1.5)	2 (0.7)	6 (1.1)
Dyspnea	0	5 (1.8)	5 (0.9)

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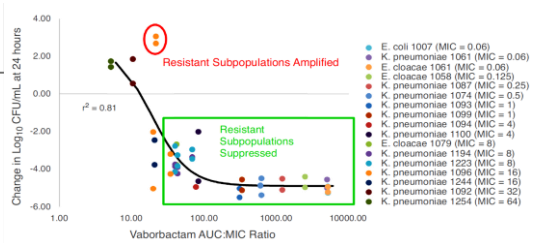
PENEM/BLI KOMBINATIONEN
Meropenem/Vaborbactam

Pathogen	No. of isolates	MEV MIC_{90} µg/mL	MEV %S US FDA	MEM MIC_{90} µg/mL	MEM %S CLSI/EUCAST	TZP MIC_{90} µg/ml	TZP %S CLSI/EUCAST
Enterobacteriaceae	46,769	0.03 to 0.06	98.7–100	0.06	96.6–98.7/96.9–98.4	8–16	92.0–93.2/88.8–89.0
Klebsiella pneumonia	5876	0.03–0.12	97.0–100	0.03–0.12	88.3–94.3/93.0–95.0	32 to > 64	87.8–88.2/80.7–82.4
Escherichia coli	11,514	≤ 0.015 to 0.03	99.8–100	0.03	99.7–99.8/99.7	8	94.7–95.7/91.2–93.3
Enterobacter cloacae spp.	2572	0.03	99.8–100		97.2/NR		
CRE	1003	0.5–32[d]	66.2–100[e]	> 32	0–3.1/6.0–10.4	> 64 to > 128	0–3.0/0–6.7
Serine-CPE	315	1	97.8	> 64	2.2/7.3		
MDR	1210	1		32	77.7/80.2	> 64	36.6/28.7
XDR	161	32		> 32	13.0/19.9	> 64	2.5/2.5
ESBL-phenotype							
Enterobacteriaceae	99	0.12	100	16	83.8/85.9	> 64	65.7/50.5
Klebsiella pneumonia	33	0.5	100				
E. coli	148	0.03	100	0.06	83.7–96.5/NR	32	83.7/NR
KPC-producing							
Enterobacteriaceae	1404	0.5–8	99.0–99.3	> 32 to > 64	0–0.7/3.4–5.2	> 64	0.7/0.7
CRE	206	1	99.5	>32	1.9/7.3		
K. pneumonia	1207	0.5–1	96.6–98.9	>32 to > 64	0–7.0/2.4		
E. coli	56	≤ 0.03 to ≤ 0.06	100	8–16	0–19.1/38.1		
E. cloacae or *Enterobacter* spp.	68	0.12–0.25	100	≥32	0–2.6/10.3		
non-KPC-producing CRE	250	>32	31.4	> 32	1.7–3.1/1.7–5.0	> 64	5.4/4.7
CNE	63	4		16	3.2/7.9	> 64	9.5/7.9
MBL-producing CRE	111	> 32	3.8–18.6	> 32	0–8.5/0–1.7		

Dhillon, Drugs 2018

PENEM/BLI KOMBINATIONEN
Meropenem/Vaborbactam

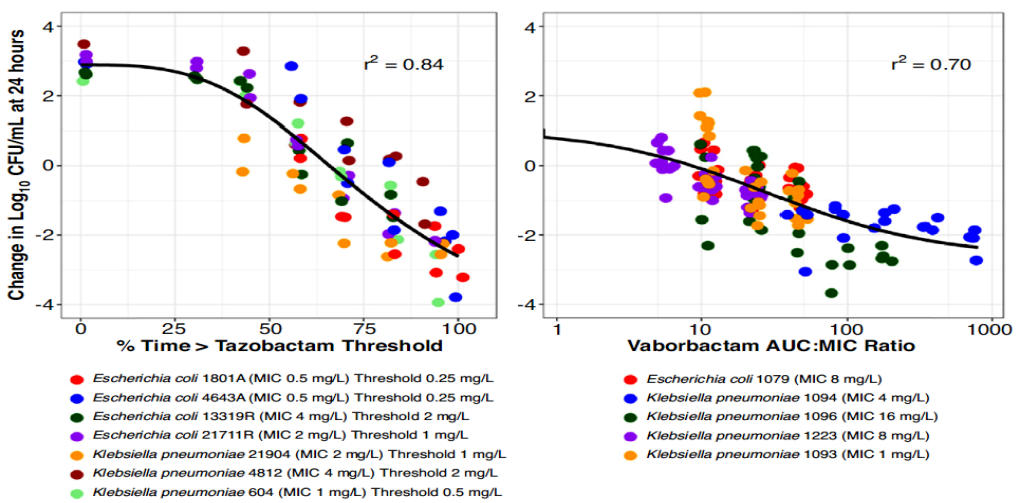
Parent and mutant	Meropenem MIC (μg/ml) in presence of VAB (μg/ml) at: Alone	2	4	8	16
KPM1275	32	≤0.06	≤0.06	≤0.06	≤0.06
KPM1852	>64	2	0.5	0.25	0.125
KPM1853	>64	16	4	1	1
KP1008	4	≤0.06	≤0.06	≤0.06	≤0.06
KPM1837	64	4	1	0.5	0.25
KPM1838	128	4	2	0.5	0.5
KPM1839	512	2	4	0.5	0.5
KP1008-12	>64	8	ND	0.5	ND



No mutations in the coding region of bla_{KPC} were identified. These data indicate that the selection of mutants with reduced sensitivity to meropenem-vaborbactam from KPC-producing *Klebsiella pneumoniae* strains is associated with previously described mechanisms involving porin mutations and the increase in the bla_{KPC} gene copy number and not changes in the KPC enzyme and can be prevented by the drug concentrations achieved with optimal dosing of the combination.

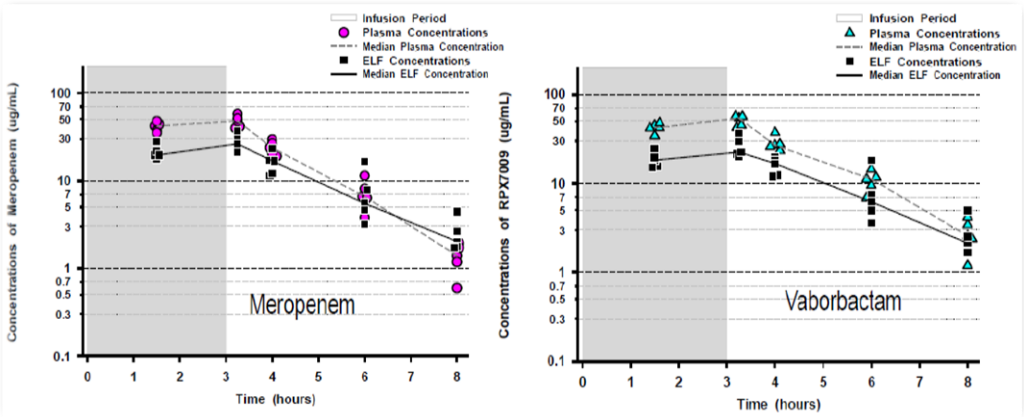
Ambrose, Curr Opin Pharmacol 2017 – Sun, Antimicrob Agents Chemother 2017

PENEM/BLI KOMBINATIONEN
Meropenem/Vaborbactam



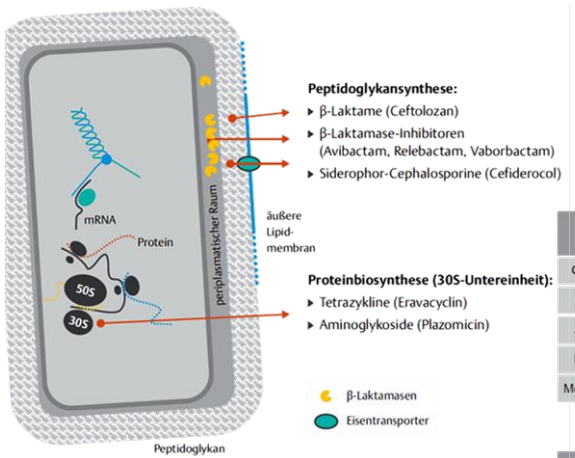
Ambrose, Curr Opin Pharmacol 2017

PENEM/BLI KOMBINATIONEN
Meropenem/Vaborbactam in der Lunge



Wenzler, Antimicrob Agents Chemother 2015

PENEM/BLI KOMBINATIONEN
Betalaktam/Betalaktamasehemmer



Peptidoglykansynthese:
- β-Laktame (Ceftolozan)
- β-Laktamase-Inhibitoren (Avibactam, Relebactam, Vaborbactam)
- Siderophor-Cephalosporine (Cefiderocol)

Proteinbiosynthese (30S-Untereinheit):
- Tetrazykline (Eravacyclin)
- Aminoglykoside (Plazomicin)

β-Laktamasen
Eisentransporter

β-Laktam/BLI-Kombinationen	Zusatznutzen: gram-positive MRE MRSA	Zusatznutzen: gram-positive MRE VRE	Zusatznutzen: gram-negative MRE Acinetobacter baumannii	Zusatznutzen: gram-negative MRE Pseudomonas aeruginosa	Zusatznutzen: gram-negative MRE Enterobacteriaceae	Inhibition: β-Laktamase-Gruppe nach Ambler A: ESBL	Inhibition: A: Carbapenemase	Inhibition: B: Metallo-β-Laktamase	Inhibition: C: AmpC-Cephalosporinase	Inhibition: D: OXA-Carbapenemase
Ceftolozan/Tazobactam	r	r	r	ja	ja	ja	–	–	–	–
Ceftazidim/Avibactam	r	r	r	ja	ja	ja	ja	–	ja	ja
Aztreonam/Avibactam	r	r	r	–	ja	ja	ja	ja	ja	ja
Imipenem/Relebactam	r	r	–	–	ja	ja	ja	–	–	–
Meropenem/Vaborbactam	r	r	–	–	ja	ja	ja	–	–	–
Stabilität										
Cefiderocol	r	r	ja	ja	ja	ja	ja	ja	ja	ja

Probst-Kepper, Anästhesiol Intensivmed Notfallmed Schmerzther 2018

PENEM/BLI KOMBINATIONEN
Zulassungsstudien im Überblick

IMIPENEM/RELEBACTAM

- **RESTORE-IMI 1**
  - cIAI
  - cUTI
  - HABP/VABP
- **RESTORE-IMI 2**
  - HABP/VABP

- **Dosierung**
  - 4 x 0.5/0.5/0.5 g

MEROPENEM/VABORBACTAM

- **TANGO I**
  - cUTI
- **TANGO II**
  - Bakteriämie
  - cIAI
  - cUTI
  - Pyelonephritis
  - HABP/VABP
- **Dosierung**
  - 3 x 1.0/1.0 g

PENEM/BLI KOMBINATIONEN
BL/BLI-Kombinationen im Vergleich

		Ceftazidim/ Avibactam	Ceftolozan/ Tazobactam	Imipenem/ Relebactam	Meropenem/ Vaborbactam	Colistin	Cefiderocol (S-649266)
Pseudomonas aeruginosa	Pseudomonas aeruginosa, **Wildtyp**						
	Pseudomonas aeruginosa, **AmpC+**						
	Pseudomonas aeruginosa **Porinverlust** (oprD-loss)						
	Pseudomonas aeruginosa **Effluxpumpen**						
	Pseudomonas aeruginosa **Carbapenem-R (Carbapenemase-negativ)**						
	Pseudomonas aeruginosa, **MDR**						
	Pseudomonas aeruginosa, **XDR**						
	Pseudomonas aeruginosa, **MBL+**						
Enterobacteriaceae spp.	Enterobacteriaceae spp., **Wildtyp**						
	Enterobacteriaceae spp., **ESBL+**						
	Enterobacteriaceae spp., **OXA-48-like+**						
	Enterobacteriaceae spp., **KPC+**						
	Enterobacteriaceae spp., **Carbapenem-R (Carbapenemase-negativ)**						
	Enterobacteriaceae spp. **MBL+ (VIM, IMP, NDM)**						
Acineto-bacter	Acinetobacter baumannii, **Wildtyp**						
	Acinetobacter baumannii, **Carbapenem-R**						
Stenotro-phomonas	Stenotrophomonas maltophilia, **Wildtyp**						
	Stenotrophomonas maltophilia **Carbapenem-R**						

In-vitro-Aktivität >80% In-vitro-Aktivität 50–80% In-vitro-Aktivität <50% Keine Daten verfügbar

* Proteus spp., Neisseria spp., Serratia spp., Providencia spp., Burkholderia pseudomallei, Morganella morganii besitzen gegenüber Colistin eine natürliche Resistenz

Thalhammer, Jatros Infektiologie 2017

PENEM/BLI KOMBINATIONEN

Mein persönliches Fazit

- Multiresistenz bei Enterobakterien zunehmend
- Pseudomonas aeruginosa-Resistenz hoch
- Piperacillin/Tazobactam keine Penem-Alternative
- BLI-Spektrum mit großer Spannbreite
- Dosierung auch bei BL/BLI ausreichend hoch wählen
- Penem/BLI mit guter Lungenpenetration
- Individualisierte (Keim&Patient) Therapie erforderlich

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www.antibiotika-app.eu