BETALAKTAMASEINHIBITOREN

STELLENWERT DER NEUEN BL/BLI-KOMBINATIONEN FÜR DIE KALKULIERTE INITIALTHERAPIE

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DIE WILL-HABEN-APP

HINWEIS

Wertes Auditorium,

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

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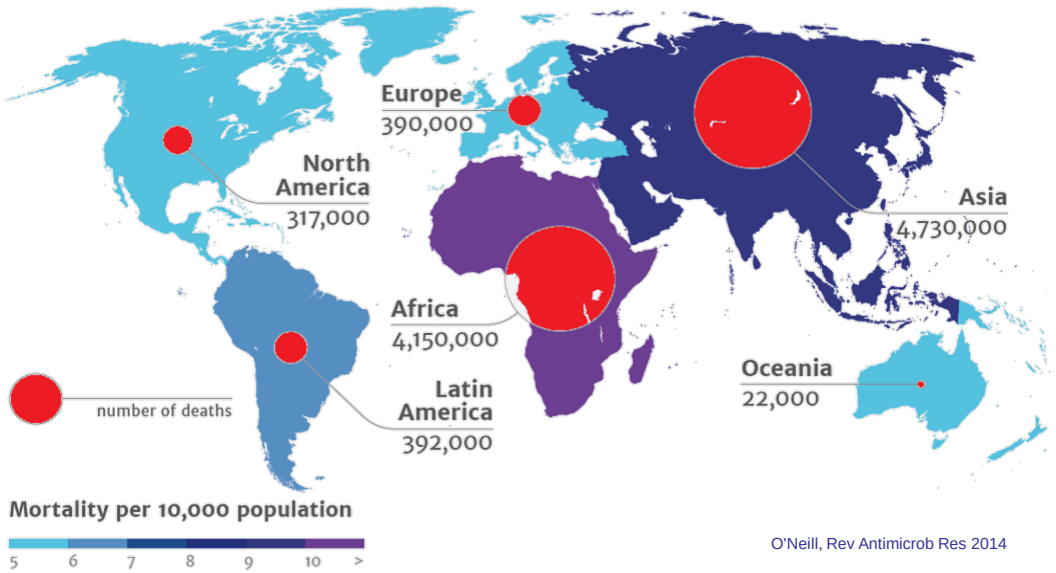
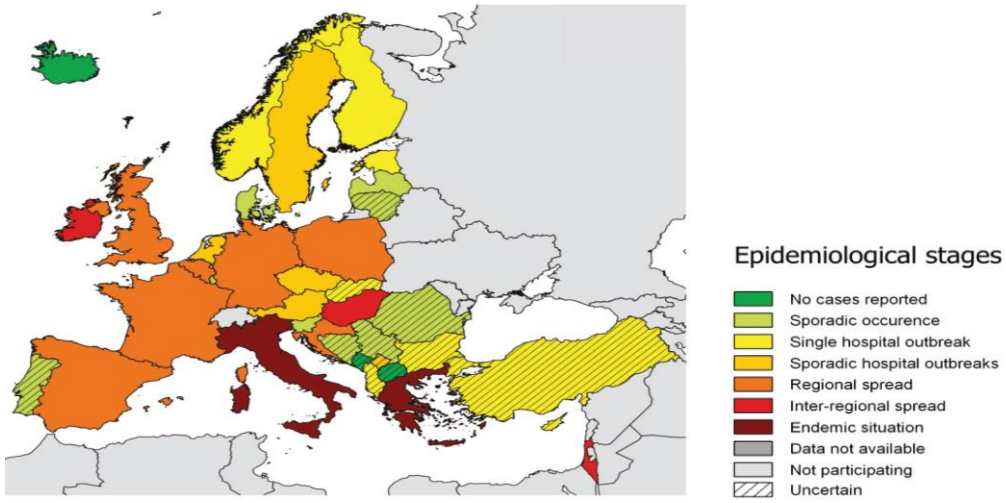
BETALAKTAMASEINHIBITOREN
Globale Mortalität



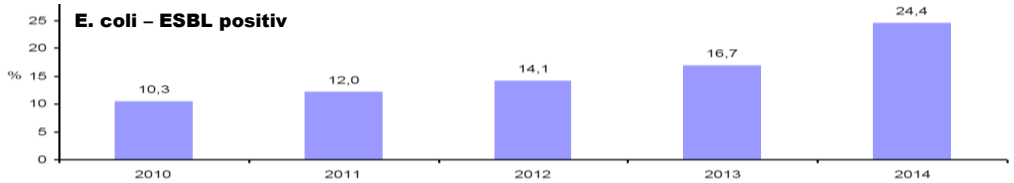
O'Neill, Rev Antimicrob Res 2014

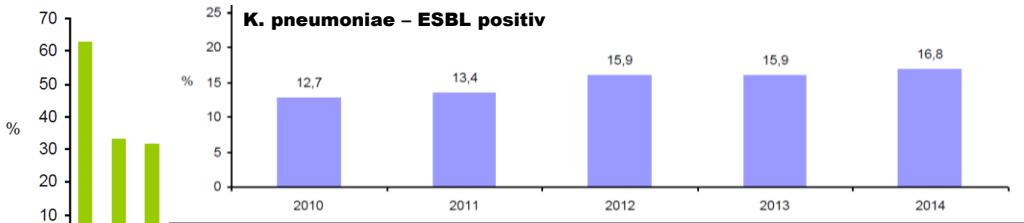
BETALAKTAMASEINHIBITOREN
CPE in Europa 2013



EuSCAPE Projekt – ECDC 2013

BETALAKTAMASEINHIBITOREN
ESBL & CPE in Österreich 2014





	GR	IT	RO	MT	BG	CY	SK	ES	PT	LV	LU	LT	HU	HR	SI	UK	DE	AT	IE	BE	FR	DK	NL	CZ	EE	FI	NO	SE
2014	62,3	32,9	31,5	9,9	7,2	5,0	2,6	2,3	1,8	1,7	1,5	1,3	1,1	0,9	0,9	0,8	0,7	0,6	0,6	0,5	0,5	0,2	0,2	0,1	0,0	0,0	0,0	0,0

AURES 2014

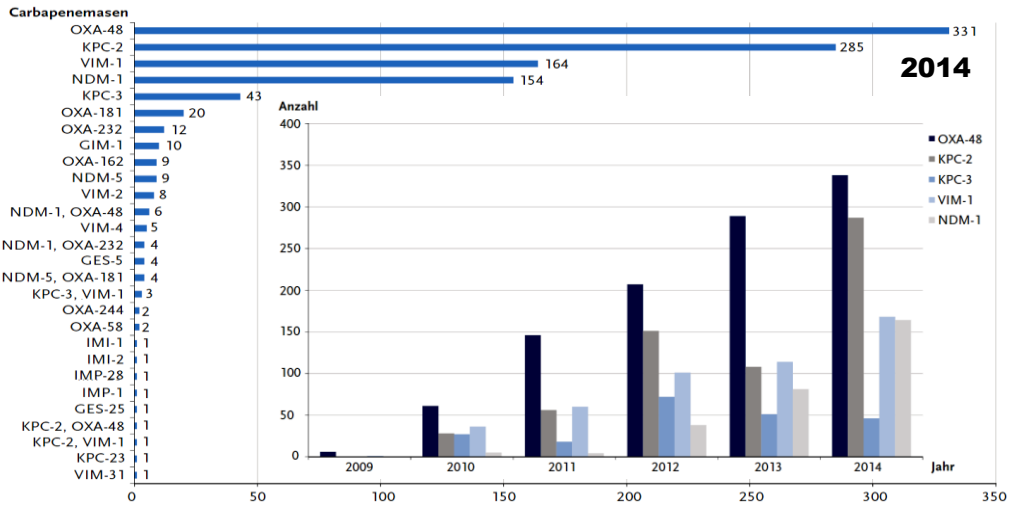
BETALAKTAMASEINHIBITOREN
Carbapenemase-positiven Isolate

	Anzahl der getesteten Isolate	Anteil der Carbapenemase-produzierenden Isolate
Enterobacteriaceae	2.677	1.240 (46,3 %)
E. coli	399	177 (44,4 %)
K. pneumoniae	1.247	672 (53,9 %)
E. cloacae	358	98 (27,4 %)
E. aerogenes	199	15 (7,5 %)
andere *Enterobacteriaceae*	474	278 (58,7 %)
P. aeruginosa	1.288	312 (24,2 %)
A. baumannii	564	525 (93,1 %)

Kaase, Epidemiolog Bulletin 2016

BETALAKTAMASEINHIBITOREN

Carbapenemasen bei Enterobacteriaceae



Kaase, Epidemiolog Bulletin 2016

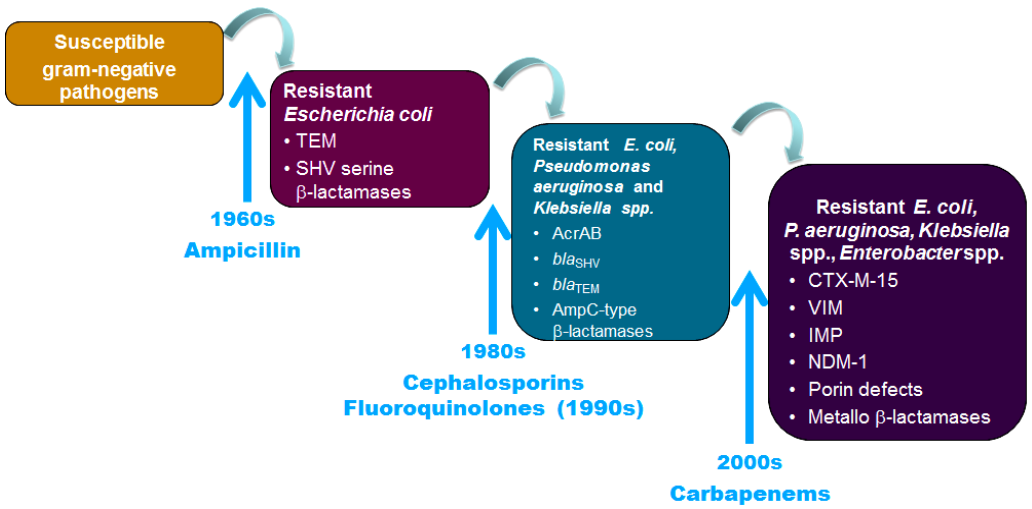
BETALAKTAMASEINHIBITOREN

Betalaktame & Selektion

Penicillin	→	Staphylokokken-Penicillinase
Aminopenicilline	→	Staphylokokken-Penicillinase, TEM-1, TEM-2, SHV-1
Aminopenicilline/ β-Lactamase-Hemmer	→	Überproduktion von TEM-1, TEM-2, SHV-1
Cephalosporine 2. – 4. Generation	→	ESBL, Überproduktion von AmpC
Carbapenem	→	Carbapenem-hydrolysierende β-Lactamasen in Kombination mit anderen Resistenzmechanismen

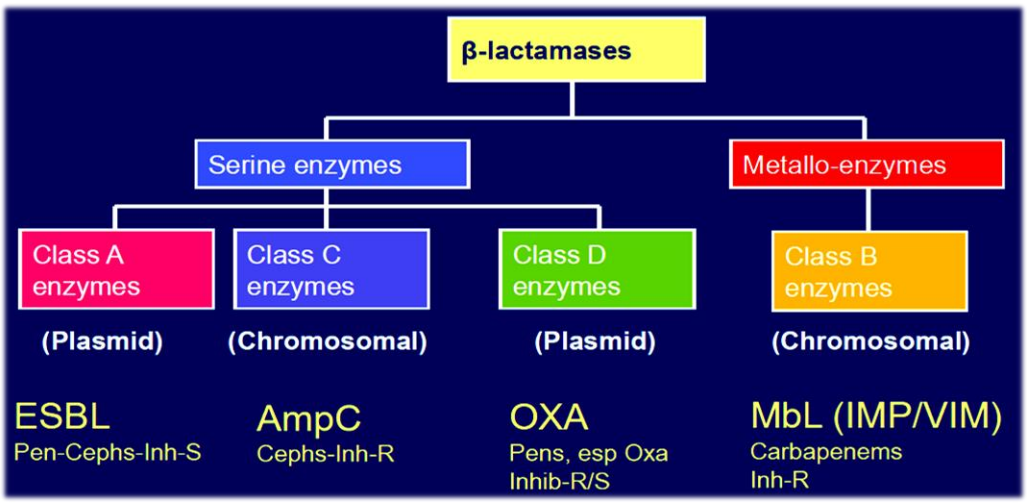
Theuretzbacher, Pharm unserer Zeit 2006

BETALAKTAMASEINHIBITOREN
Evolution der Gram-neg Resistenz



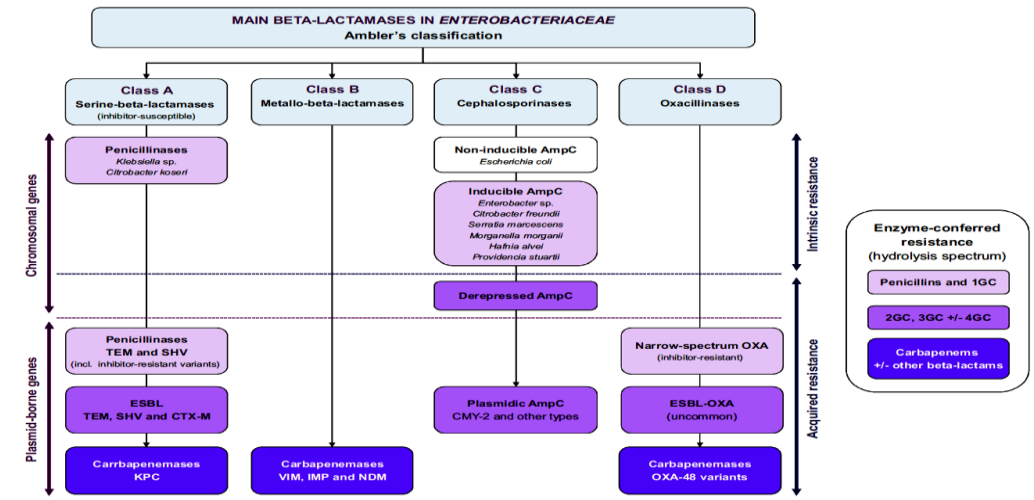
Livermore, CID 2002 – Hawkey, AAC 2008 – Hawkey, JAC 2009 – Bush, AAC 2010 – Olivares, Front Microbioal 2013

BETALAKTAMASEINHIBITOREN
Klassifikation der Betalaktamasen



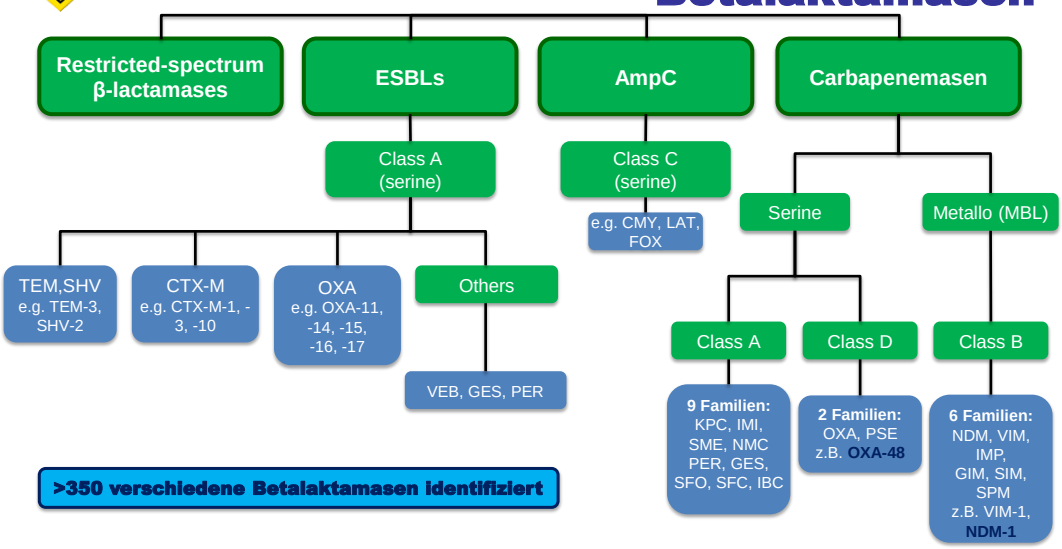
Bush, Rev Inf Dis 1987 – Bush, Antimicrob Agents Chemother 1959 – Bush, Curr Opin Investig Drugs 2002

BETALAKTAMASEINHIBITOREN
Betalaktamasen bei Enterobakterien



Ruppe, Ann Intensive Care 2015

BETALAKTAMASEINHIBITOREN
Betalaktamasen

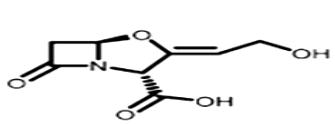


Bradford, Clin Microbiol Rev 2001 – Jacoby, Clin Microbiol Rev. 2009 – Stuart, Int J Antimicrob Agents. 2010

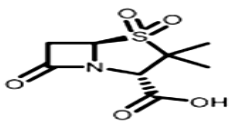
BETALAKTAMASEINHIBITOREN
Therapieoptionen bei Betalaktamasen

	Broad Spectrum			Expanded Spectrum			AmpC	Carbapenemase		
	TEM/	SHV	OXA	TEM/SHV	CTX-M	OXA		KPC	MBL	OXA
Class	A		D	A	A	D	C	A	B	D
Inhibition by Clavulanic Acid										
Penicillins										
Oxacilin										
Narrow Spectrum Cephalosporins										
Cephamycins										
Oxyimino-cephalosporins										
Cefepime										
Monobactam										
Carbapenems										
Polymyxin E										

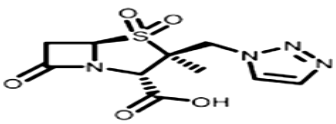
BETALAKTAMASEINHIBITOREN
Betalaktamaseinhibitore



clavulanic acid

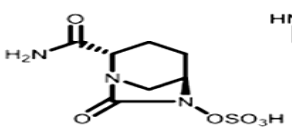


sulbactam

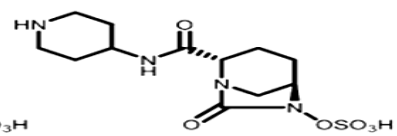


tazobactam

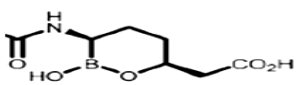
Hemmung einiger Klasse A Betalaktamasen



avibactam



relebactam



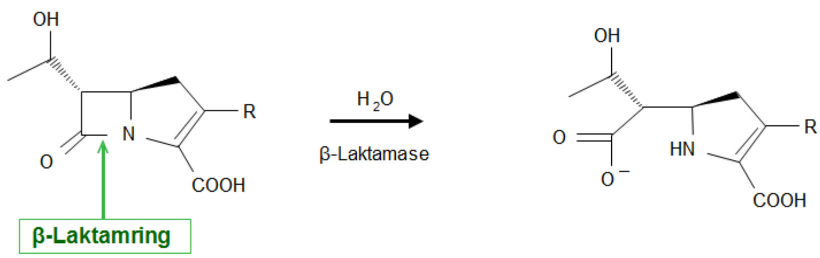
RXP7009

Hemmung von Klasse A & C Betalaktamasen: ESBL, AmpC, KPC
Variable Hemmung von Klasse D Betalaktamasen
KEINE HEMMUNG VON KLASSE B BETALAKTAMSEN

BETALAKTAMASEINHIBITOREN
Wirkprinzip der Betalaktamasen

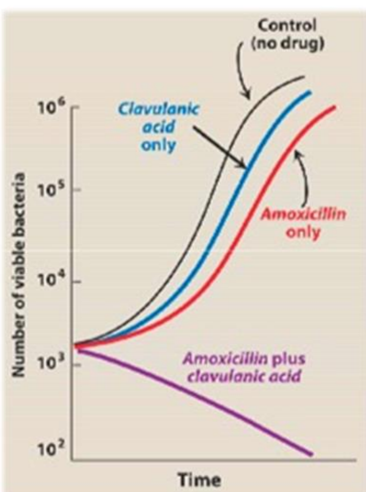
Betalaktamasen inaktivieren Betalaktame durch Aufbrechen des Betalaktamringes

AKTIVES Betalaktamantibiotikum **INAKTIVIERTES** Betalaktamantibiotikum



Ludwig, Urologe 2014

BETALAKTAMASEINHIBITOREN
BLI-Aktivität



Enzyme class[a]	Organism[b]	Inhibitory Activity[c] Tazobactam	Clavulanic acid	Sulbactam
1a	Enterobacter cloacae	+	0	+
1b	Escherichia coli	+	0	0
1c	Bacteroides fragilis Proteus vulgaris	+ + +	+ +	+ +/+ + +
1d	Pseudomonas aeruginosa	+	0	+
II	Proteus mirabilis	+ + +	+ + +	+ +
III	E.coli TEM-1 E.coli SHV-1	+ + + + + +	+ + +++	0 0
IV	Klebsiella pneumoniae	+ + +	+ + +	+
V	E.coli OXA-1 E.coli PSE-1 Staphylococcus aureus	+ +++ ++	+ +++ ++	+ ++ +

[a] Based on Richmond and Sykes Classification [b] Enzymes stated were those produced by organism studied

[c] + + + = IC50 < 0.05 mg/L + + = IC50 > 0.05 - < 0.5 mg/L + = IC50 > 0.5 - < 5 mg/L;

BETALAKTAMASEINHIBITOREN
Betalaktamseinhibitor Turnover

- **Zahl der Moleküle (t_n), die bis zu einer irreversiblen Hemmung der Betalaktamase verbraucht werden.**

β-Lactamase	Ambler class	Clavulanate			Sulbactam			Tazobactam		
		K_I (μM)	IC_{50} (nM)	t_n	K_I (μM)	IC_{50} (nM)	t_n	K_I (μM)	IC_{50} (nM)	t_n
TEM-1	A	0.1	60	160	1.6	900	10,000	0.01	97	140
SHV-1	A	1	12	60	8.6	12,000	13,000	0.07	150	5
SHV-5	A		20			1,800			80	
PC1	A		30	1		80			27	1
CTX-M-2	A		200			2,100			20	
CcrA	B		>500,000	>500,000		>500,000			400,000	4,000
P99	C		>100,000	>500,000		5,600			8.5	50
CMY-2	C	4,365			101			50		
OXA-1	D		1,800			4,700		380	1400	
OXA-2	D		1,400		0.1	140			10	

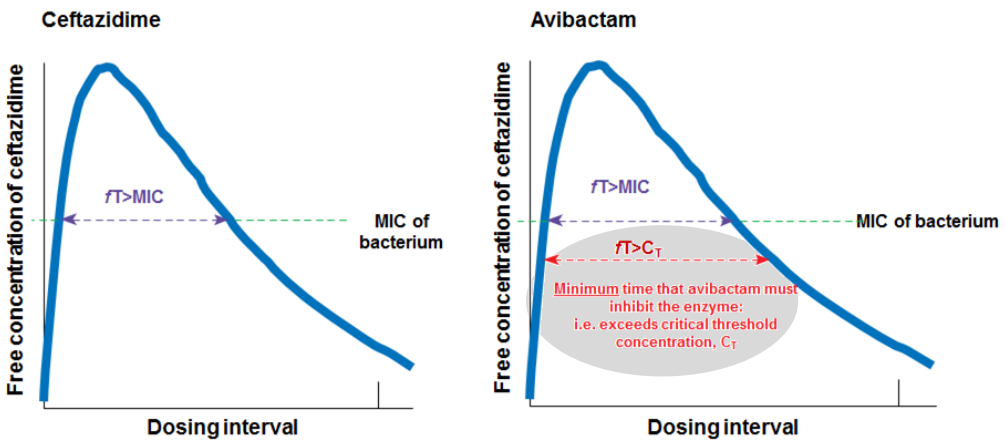
Avibactam

1 – 5 Moleküle notwendig, um 1 BL-Molekül zu hemmen

Stachyra, Antimicrob Agents Chemother 2009 – Drawz, Clin Microbiol Rev 2010 – Toussaint, Ann Pharmacother 2014

BETALAKTAMASEINHIBITOREN
Pharmakodynamik von BL/BLI

BLI muss Betalaktamase während BL-Aktivität inaktivieren



Berkhout, ICAAC 2013; Poster A-1023 – Coleman, Antimicrob Agents Chemother 2014

BETALAKTAMASEINHIBITOREN
Betalaktamaseninhibitoren bei ESBL

- **Inoculum-Effekt (Bakterienlast inaktiviert BLBLI)**
  - **in vitro ausgeprägt bei Piperacillin/Tazobactam**
  - **in vitro gering bei Amoxicillin/Clavulansäure**
  - **in vivo-Bedeutung nicht geklärt**
- **PK/PD-Indizes bei BLBLI nicht immer erreicht**

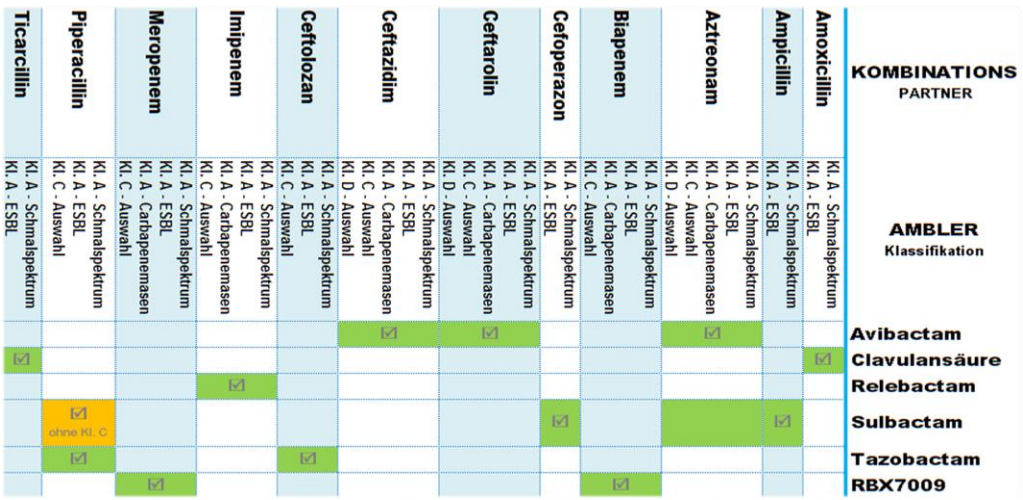
Bonfiglio, Duagn Microbiol Infect Dis 1994 – Thomson, Antimicrob Agents Chemother 2001 – López-Cerero, Clin Microbiol Infect 2010 – Nguyen, J Antimicrob Chemother 2014 – Harris, Lancet Infect Dis 2015

BETALAKTAMASEINHIBITOREN
Betalaktamasen

Serine-ß-Laktamasen	Metallo-ß-Laktamasen	Serine-ß-Laktamasen	Serine-ß-Laktamasen
Klasse A	Klasse B	Klasse C	Klasse D
Beta-Laktamasen mit erweitertem Wirkungsspektrum			
– TEM – SHV – **CTX-M**		– AmpC – CMY, DHA – MOX, FOX	– OXA-2, -9
Carbapenemasen			
– KPC – GES – SME	– VIM – IMP, NDM – GOB, GIM		– OXA-48 – OXA-23, -24, -58

Forstner, Krankenhaushygiene up2date 2014

BETALAKTAMASEINHIBITOREN
BLI-Kombinationen & Aktivität

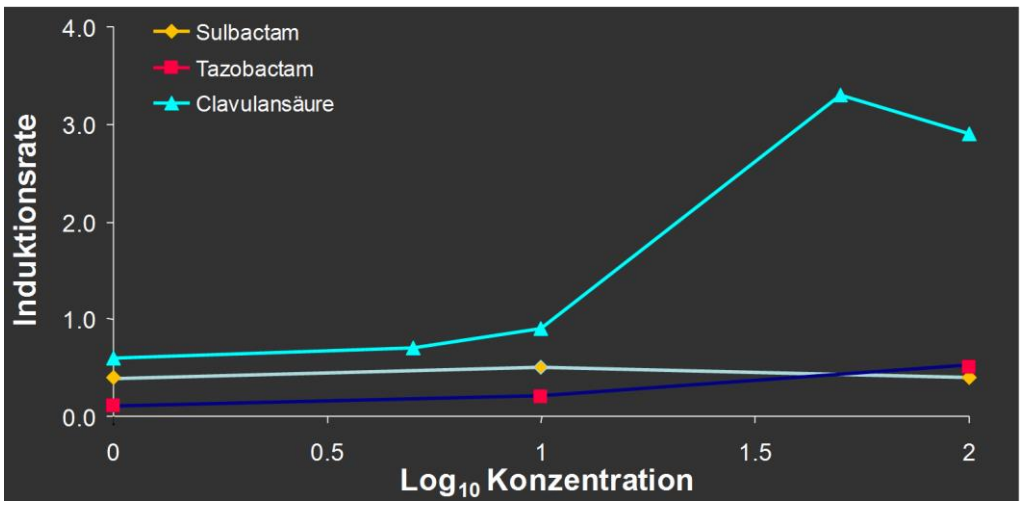


Toussaint, Ann Pharmacother 2014

BETALAKTAMASEINHIBITOREN
BLI-Kombinationen

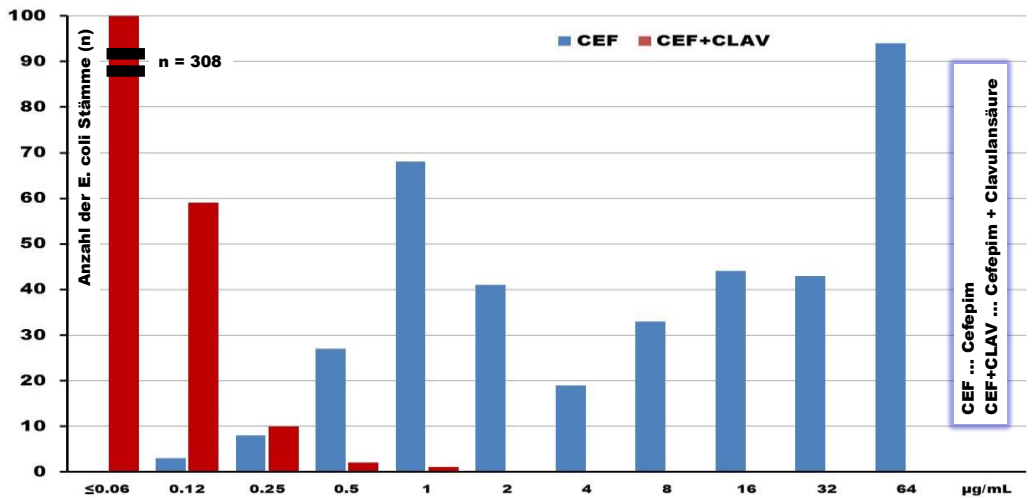
- **Clavulansäure**
  - Amoxicillin (Augmentin®) ➲ ambulant erw. Pneumonie ⊙ 3 x 4.4 g i.v.
  - Ticarcillin ➲ Pseudomonas ⊙ 3 x 3.1 g i.v.
- **Sulbactam**
  - Ampicillin (Unasysn®) ➲ Harnwegsinfektion ⊙ 3 x 6.0 g i.v.
- **Tazobactam**
  - Piperacillin (Tazonam®) ➲ Pseudomonasinfektion ⊙ 3 x 4.5 g i.v.
  - Ceftolozan/Tazobactam (Zerbaxa®) ➲ Pseudomonasinfektion ⊙ 3 x 3.0 g i.v.
- **Avibactam**
  - Ceftazidim/Avibactam (Avycaz®) ➲ Pseudomonasinfektion ⊙ 3 x 2.5 g i.v.

BETALAKTAMASEINHIBITOREN
Induktion von β-Laktamasen



Moosdeen, Rev Infect Dis 1986

BETALAKTAMASEINHIBITOREN
Clavulansäure – ESBL-Aktivität



Livermore, J Antimicrob Chemother 2008

® Augmentin

BETALAKTAMASEINHIBITOREN
Amoxicillin/Clavulansäure & ESBL

Wachstum von:
01 Escherichia coli ESBL **Gesamtkeimzahl:** > 10E5 KBE/ml

Empfindlichkeitsprüfung mit Agardiffusionstest:

	Keimnr.:	01
03B	Ampicillin	-
04D	Amoxicil./Clavulansre.	+
05	Mecillinam	-
07	Aztreonam	-
08A	Meropenem	+
08C	Ertapenem	+
08H	Cefalexin	-
09B	Cefuroxim	-
10A	Cefoxitin	+
13	Cefotaxim	-
15A	Cefepim	-
16	Gentamicin	-
19	Amikacin	+
25	Fosfomycin	+
28	Trimethoprim	-
30	Ciprofloxacin	-
31	Nitrofurantoin	+
32	Colistin	+

+: empfindlich, -: resistent, X: mäßig empfindlich, N: nicht indiziert

Penicillins[1]	MIC breakpoint (mg/L) S ≤	MIC breakpoint (mg/L) R >	Disk content (µg)	Zone diameter breakpoint (mm) S ≥	Zone diameter breakpoint (mm) R <
Benzylpenicillin	-	-		-	-
Ampicillin	8[1]	8	10	14[4,8]	14[8]
Ampicillin-sulbactam	8[1,2]	8[2]	10-10	14[4,8]	14[8]
Amoxicillin	8[1]	8	-	Note[6]	Note[6]
Amoxicillin-clavulanate	8[1,3]	8[3]	20-10	19[4,8]	19[8]
Amoxicillin-clavulanate (uncomplicated UTI only)	32[1,3]	32[3]	20-10	16[4,8]	16[8]
Piperacillin	8	16	30	20	17
Piperacillin-tazobactam	8[4]	16[4]	30-6	20	17
Ticarcillin	8	16	75	23	23
Ticarcillin-clavulanate	8[3]	16[3]	75-10	23	23
Phenoxymethylpenicillin	-	-		-	-
Oxacillin	-	-		-	-
Cloxacillin	-	-		-	-
Dicloxacillin	-	-		-	-
Flucloxacillin	-	-		-	-
Mecillinam (uncomplicated UTI only)	8[5]	8[5]	10	16[8,9]	16[8,9]

Breitspektrum-Betalaktamase nachgewiesen.
Auch bei Vorliegen einer in-vitro Empfindlichkeit gegenüber Penicillin/Betalaktamaseinhibitor-Kombinationen ist die klinische Wirksamkeit nicht gewährleistet.

Andes, Clin Microbiol Infect 2005 – Mikrobiologie AKH & MU Wien – www.eucast.org

BETALAKTAMASEINHIBITOREN
AmpC – Carbapenem vs PipiTaz

Carbapenems versus alternative antibiotics for the treatment of bloodstream infections caused by *Enterobacter*, *Citrobacter* or *Serratia* species: a systematic review with meta-analysis

Objectives: This systematic review and meta-analysis compared effects of different antibiotics on mortality in patients with bloodstream infections caused by Enterobacteriaceae with chromosomal AmpC β-lactamase.

Methods: Databases were systematically searched for studies reporting mortality in patients with bloodstream infections caused by AmpC producers treated with carbapenems, broad-spectrum β-lactam/β-lactamase inhibitors (BLBLIs), quinolones or cefepime. Pooled ORs for mortality were calculated for cases that received monotherapy with these agents versus carbapenems. Registration: PROSPERO international prospective register of systematic reviews (CRD42014014992; 18 November 2014).

Results: Eleven observational studies were included. Random-effects meta-analysis was performed on studies reporting empirical and definitive monotherapy. In unadjusted analyses, no significant difference in mortality was found between BLBLIs versus carbapenems used for definitive therapy (OR 0.87, 95% CI 0.32–2.36) or empirical therapy (OR 0.48; 95% CI 0.14–1.60) or cefepime versus carbapenems as definitive therapy (OR 0.61; 95% CI 0.27–1.38) or empirical therapy (0.60; 95% CI 0.17–2.20). Use of a fluoroquinolone as definitive therapy was associated with a lower risk of mortality compared with carbapenems (OR 0.39; 95% CI 0.19–0.78). Three studies with patient-level data were used to adjust for potential confounders. The non-significant trends favouring non-carbapenem options in these studies were diminished after adjustment for age, sex and illness severity scores, suggestive of residual confounding.

Conclusions: Despite limitations of available data, there was no strong evidence to suggest that BLBLIs, quinolones or cefepime were inferior to carbapenems. The reduced risk of mortality observed with quinolone use may reflect less serious illness in patients, rather than superiority over carbapenems.

Harris, J Antimicrob Chemother 2016

BETALAKTAMASEINHIBITOREN
pro&con BLBLI bei ESBL

Arguments in favour

- By definition, Ambler class A ESBL producers are inhibited by antimicrobials that inactivate β lactamases such as clavulanate or tazobactam
- Emerging data from some large cohort studies and a meta-analysis support the safety and efficacy of BLBLIs
- Drugs used regularly against Enterobacteriaceae expressing class A β lactamases (eg, TEM-1 in ampicillin-resistant *Escherichia coli*, SHV-1 in *Klebsiella pneumoniae*), and other β-lactamase-producing species (eg, *Haemophilus influenzae*, *Staphyloccoccus 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 BLBLIs 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 cephalopsorins, carbapenems, or quinolones

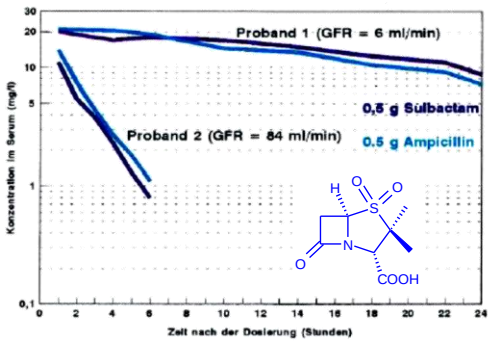
Arguments against

- Carbapenems remain stable to ESBLs and are recommended as first-line therapy for serious infections
- Scarce published clinical experience on the efficacy of BLBLIs against ESBL producers causing infections outside the urinary tract
- An inoculum effect shown in mouse models, which might limit efficacy
- Increasing resistance to BLBLIs in ESBL producers, especially *K pneumoniae*, thus limiting efficacy in empirical therapy
- Overexpression of β lactamases (including by other non-ESBLs) that might overwhelm the inhibitor component
- No head-to-head randomised trials to assess BLBLIs 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

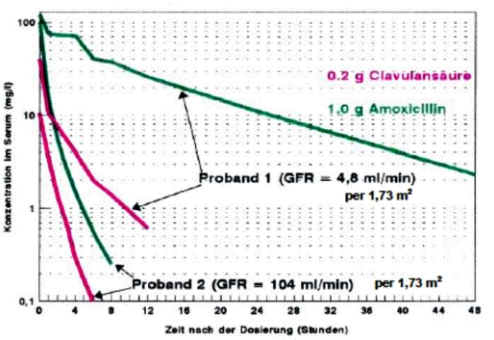
Harris, Lancet Infect Dis 2015

BETALAKTAMASEINHIBITOREN
Sulbactam

- **Sulbactam**
  - **BLI als Substanz (Combactam®) erhältlich und kombinierbar**
  - **Kombination mit Cephalosporin od Piperacillin nicht sinnvoll**



Dosierung: Ampicillin 500 mg (i.v.), Sulbactam 500 mg (i.v.)

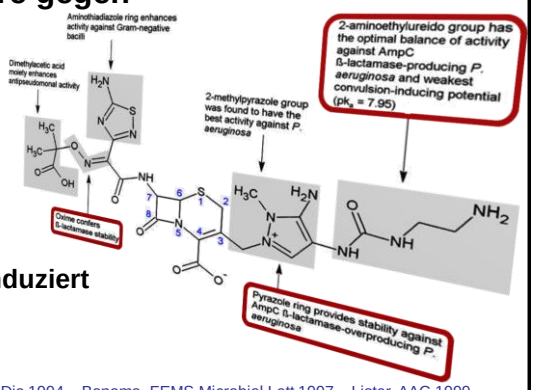


Dosierung: Amoxicillin 1000 mg (i.v.), Clavulansäure 200 mg (i.v.)

Wright, J Antimicrob Chemother 1983 – Horber, Antimicrob Agents Chemother 1986

BETALAKTAMASEINHIBITOREN
Tazobactam

- reduziert renale Sekretion von Piperacillin
- schützt Piperacillin vor Hydrolyse
- 10-fach aktiver als Clavulansäure gegen TEM
- Inoculum-Effekt
- Wildtyp AmpC induzierende Enterobakterien
  - Mittel der Wahl (bzw. Ticarcillin)
  - Vermeidung von Ceph III
  - Vermeidung von Clavulansäure (induziert AmpC bei PAE)



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 – Zhanel, Drugs 2014 – Harris, Lancet Infect Dis 2015 – Ruppé, Ann Intensive Care 2015

BETALAKTAMASEINHIBITOREN
Ceftolozan/Tazobactam

Mean 50% inhibitory concentration of ceftolozane, ceftazidime and imipenem for *Pseudomonas aeruginosa* penicillin-binding proteins.

PBP	Ceftolozane IC_{50} (μg/ml) ± SD	Ceftazidime IC_{50} (μg/ml) ± SD	Imipenem IC_{50} (μg/ml) ± SD
1b	0.07 ± 0.01	0.12 ± 0.03	0.13 ± 0.01
1c	0.64 ± 0.17	>2	0.08 ± 0.005
2	1.36 ± 0.56	>2	0.08 ± 0.01
3	0.02 ± 0.007	0.04 ± 0.01	0.12 ± 0.2
4	0.29 ± 0.05	1.23 ± 0.49	0.02 ± 0.01
5/6	>2	>2	0.2 ± 0.09

IC_{50}: 50% inhibitory concentration; PBP: Penicillin-binding protein; SD: Standard deviation.

	Outer membrane porin loss	β-lactamase enzyme	Efflux pump	Efflux pump
	OprD	AmpC	MexXY	MexAB
Ceftolozane	o	+	o	o
Ceftazidime	o	++++	o	++
Imipenem	++++	o/+	o	o
Meropenem	+++	o/+	o	++
Piperacillin/tazobactam	o	++++	o	+++
Cefepime	o	+++	++	++
Aztreonam	o	++	o	+++

Riera, JAC 2001 – Livermore, CID 2002– Zhanle, Drugs 2007 – Davies, JAC 2011 – Crandon, AAC 2012 – Cubist, Data on file 2014 – Bassetti, Future Microbiol 2015

BETALAKTAMASEINHIBITOREN
Ceftolozan/Tazobactam

Organism (number of isolates)	Ceftolozane/TZ $MIC_{50/90}$ (range)	Piperacillin/TZ $MIC_{50/90}$ (range)	Ceftazidime $MIC_{50/90}$ (range)	Imipenem $MIC_{50/90}$ (range)
Klebsiellapneumoniae CAZ-R (186)	4/>16 (≤0.12–>16)	32–>64 (1–>64)	64/>64 (32–>64)	≤0.5–≤0.5 (0.5–>8)
Klebsiella pneumoniae KPC producer (53)	>16/>16 (16–>16)	>64–>64 (>64)	>64/>64 (64–>64)	>8–>8 (4–>8)
Escherichia coli CAZ-R (224)	1/16 (≤0.12–>16)	16–>64 (1–>64)	64/>64 (32–>64)	≤0.5–≤0.5 (0.5–>8)
Proteus mirabilis ESBL producer (68)	1/8 (0.25–>16)	≤1–8 (0.5–>32)	≤4/>64 (≤4/>64)	2–4 (≤0.5–4)
Enterobacter spp. CAZ-R (90)	16/>16 (0.25–>16)	64–>64 (2–>64)	>64/>64 (32–>64)	≤0.5–1 (≤0.5–>8)
Citrobacter spp. CAZ-R (108)	16/>16 (0.25–>16)	64–>64 (1–>64)	>64/>64 (32–>64)	≤0.5–1 (≤0.5–8)
Pseudomonas aeruginosa CAZ-R (39)	2–64 (0.5–>128)	64–>64 (16–>64)	>64/>128 (16–>128)	1–4 (0.5–4)
Pseudomonas aeruginosa IMI-R (143)	0.5–1 (0.25–8)	16–64 (2–>64)	8/8 (2–8)	>8/>8 (8–>8)
Pseudomonas aeruginosa CAZ-R/IMI-R (213)	2/16 (0.5–>128)	>64–>64 (8–>64)	64/>128 (16–>128)	>8/>8 (8–>8)

Bassetti, Future Microbiol 2015

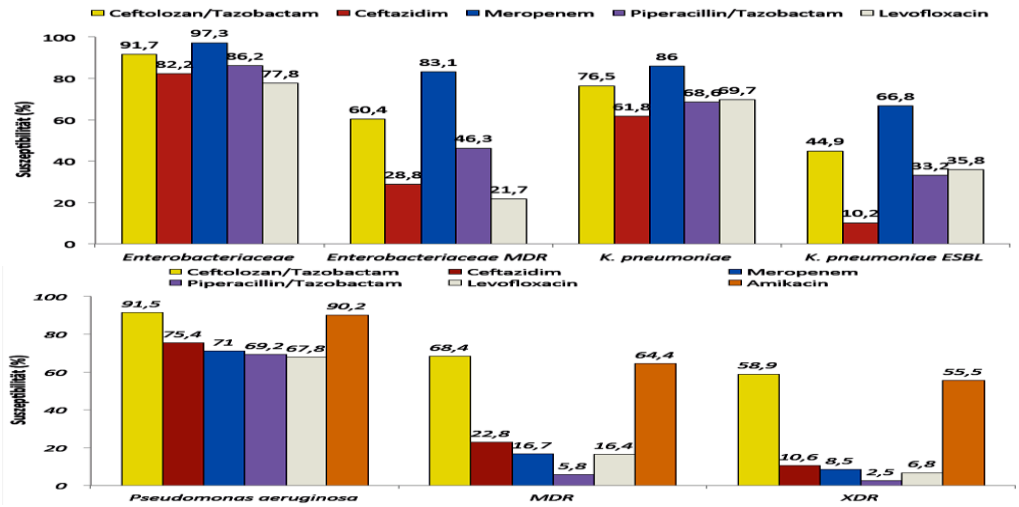
BETALAKTAMASEINHIBITOREN
Resistenzmechanismen bei *P. aeruginosa*

	äußere Membran: Verlust des Porins	β-Lactamase-enzyme	Efflux Pumpe	Efflux Pumpe
	OprD	AmpC	MexXY	MexAB
Ceftolozan	0	+	0	0
Ceftazidim	0	++++	0	++
Imipenem	++++	0/+	0	0
Meropenem	+++	0/+	0	++
Piperacillin/Tazobactam	0	++++	0	+++
Cefepim	0	+++	++	++
Aztreonam	0	++	0	+++

0: kein Einfluss auf MHK im Vergleich zum Elternstamm +: 2-fache Erhöhung der MHK im Vergleich zum Elternstamm ++: 4-fache Erhöhung der MHK im Vergleich zum Elternstamm +++: 8-fache Erhöhung der MHK im Vergleich zum Elternstamm ++++: >8-fache Erhöhung der MHK im Vergleich zum Elternstamm

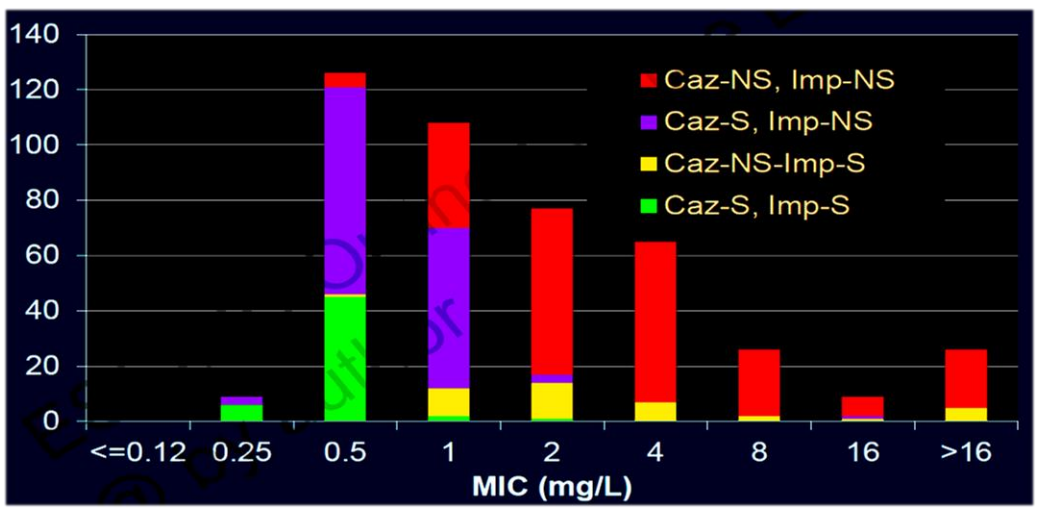
Livermore, CID 2002 – Takeda, Antimicrob Agents Chemother 2007 – Zhanel, Drugs 2007 – Riere, JAC 2011 – Crandon, AAC 2012

BETALAKTAMASEINHIBITOREN
Ceftolozan/Tazobactam



Farrell, ECCMID 2015

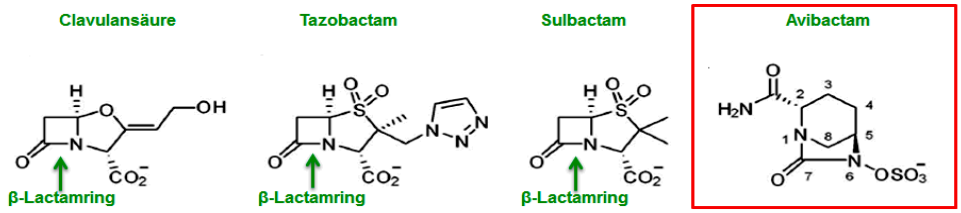
BETALAKTAMASEINHIBITOREN
Ceftolozan/Tazobactam & *P. aeruginosa*



Sader, Antimicrob Agents Chemother 2011 – Livermore, ECCMID 2015

BETALAKTAMASEINHIBITOREN
Avibactam

- **Differenzierung zu anderen BLI**
  - keine β-Laktam-Struktur
  - Wiederherstellung der Aktivität von Cetazidim und anderen Betalaktam-Antibiotika gegen Kl A, Kl C und einige Kl D Betalaktamaseinhibitoren
  - keine Induktion von Betalaktamasen
  - 50% niedrigere Wirkkonzentration notwendig



Lahiri, Antimicrob Agents Chemother 2013

BETALAKTAMASEINHIBITOREN
Ceftazidim/Avibactam im Vergleich

	IC_{50} (nM) for inhibition of β-lactamase activity		
	Avibactam	Clavulanic acid	Tazobactam
Class A			
ESBL			
TEM-1	8	130	40
TEM-1	8	58	32
SHV-4	1.5	5	120
SHV-4	3	4	55
CTX-M-15	5	12	6
CTX-M-15	5	12	6
KPC			
KPC-2	38	6500	80 000
KPC-2	170	>100 000	50 000
Class C			
P99	80	1×10^6	5000
P99	100	>100 000	1300
AmpC	128	<100 000	4600

Zhanel, Drugs 2013

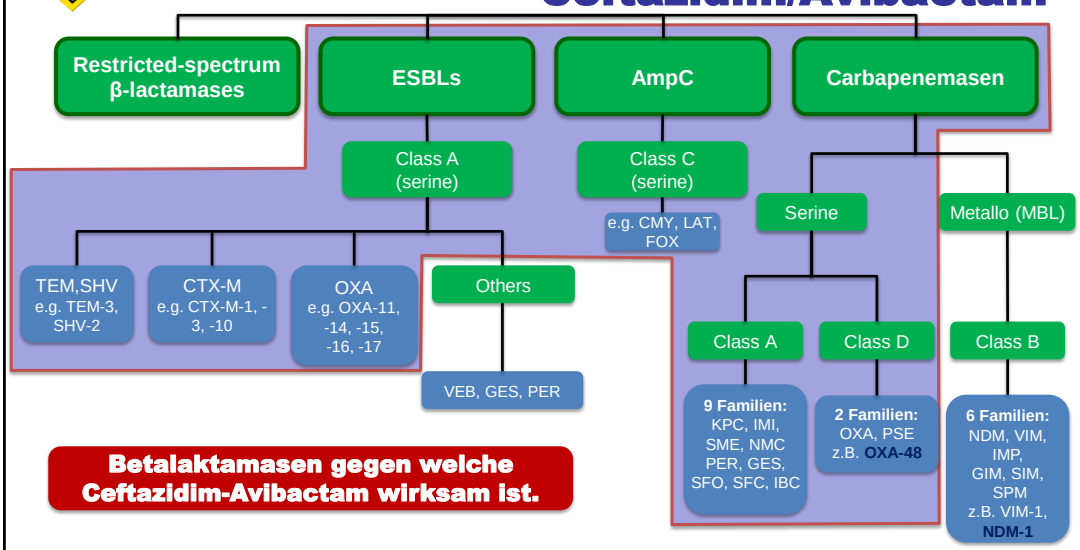
BETALAKTAMASEINHIBITOREN
Aktivität neuer BL-BLI-Kombinationen

Pathogen	Ceftazidime	Ceftazidime–avibactam	Ceftaroline	Ceftaroline–avibactam	Ceftolozane	Ceftolozane–tazobactam	(MIC$_{90}$ µg/mL) Imipenem	Imipenem MK7655
E. coli ESBL	32	0.5	>32	0.25	>32	16		
K. pneumoniae ESBL	>32	2	>32	1	>32	>16		
K. pneumoniae NS to carbapenem	>32	2	>32	2	>32	>16	64	1
E. cloacae Ceftazidime-R	>32	2	>32	1	>32	>16		
Enterobactereaceae Multiple β-lactamases	>256	4	>64	0.5				
CTX-M (538)			>32	0.25				
KPC (118)			>32	1				
SHV (50)			>32	0.5				
AmpC + CTX-M (43)			>32	2				
SHV + CTX-M (28)			>32	0.25				
SHV + KPC (18)			>32	4				
Pseudomonas aeruginosa	32	8	Not expected	Not expected	8	8	32	4

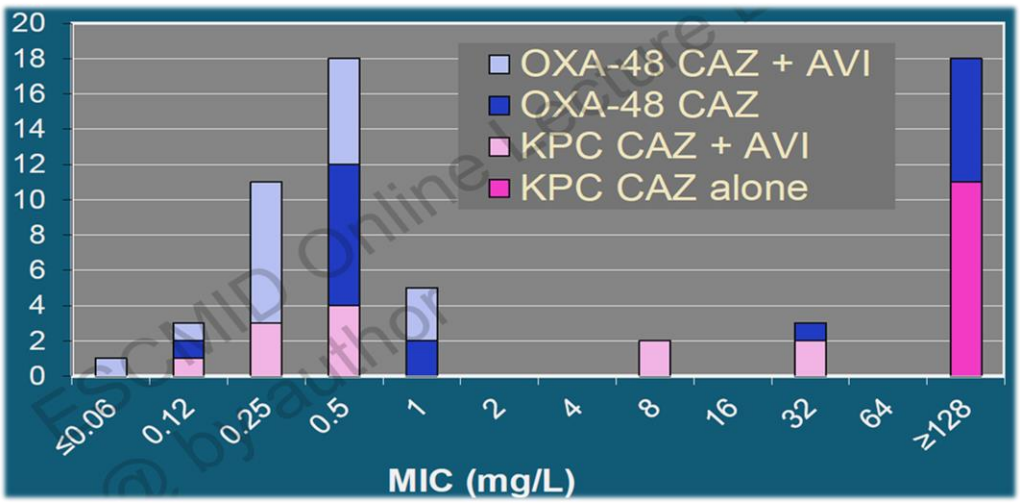
β-Lactamase	Inhibitor (IC_{50} µM) Tazobactam	Avibactam	MK7655
TEM-1	0.01	0.01	0.03
KPC-2	43.00	0.17	0.21
SHV-1	0.07	NR	0.03
SHV-4	0.06	0.003	NR
SHV-5	0.01	NR	0.36
CTX-M15	0.01	0.01	NR
AmpC (*P. aeruginosa*)	1.49	0.13	0.47
P99	12.00	0.10	0.13
Oxa (*A. baumannii*)	58.00	NR	>50

Shlaes, Ann N Y Acad Sci 2013

BETALAKTAMASEINHIBITOREN
Ceftazidim/Avibactam

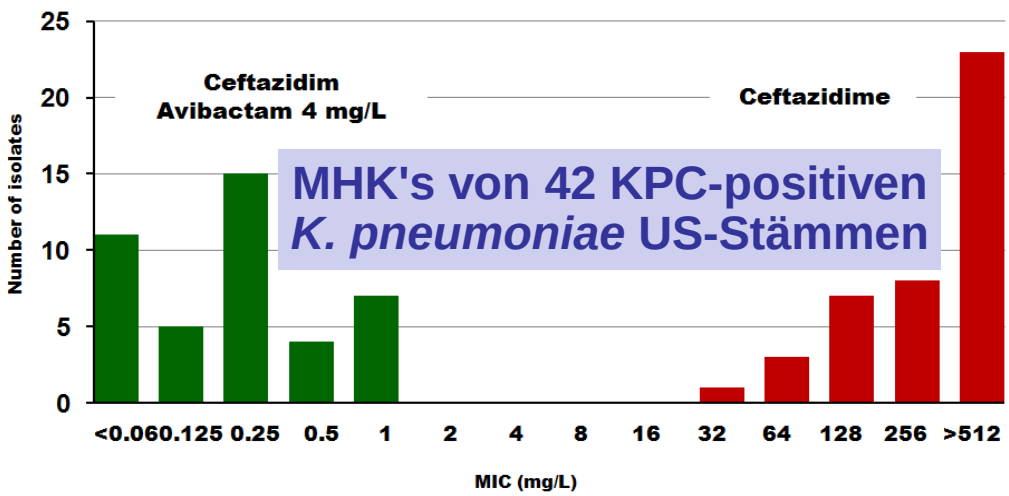


BETALAKTAMASEINHIBITOREN
Ceftazidim/Avibactam & Enterobakterien



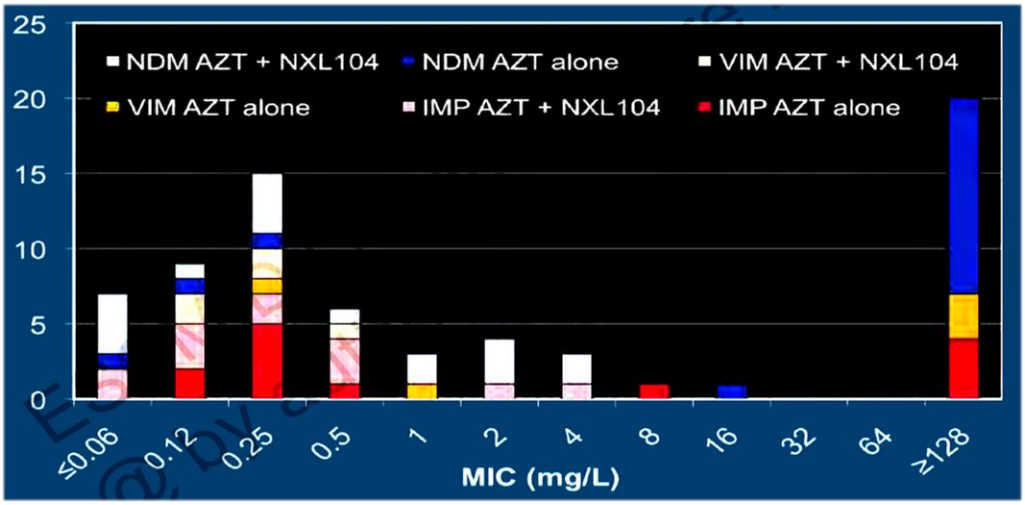
Livermore, Antimicrob Agents Chemother 2011 – Livermore, ECCMID 2015

BETALAKTAMASEINHIBITOREN
Ceftazidim/Avibactam



Endimiani, Antimicrob Agents Chemother 2009

BETALAKTAMASEINHIBITOREN
Aztreonam/Avibactam & MBL-Enterobak



Livermore, Antimicrob Agents Chemother 2011 – Livermore, ECCMID 2015

BETALAKTAMASEINHIBITOREN
BLI-Aktivität gegen Betalaktamasen

	β-Lactamase-Enzyme					
	AmpC	CTX-M	SHV	TEM	KPC	MBL
Sulbactam	-/+	+	+	+	-	-
Clavulansäure	-	+	+	+	-	-
Tazobactam	-	+	+	+	-	-
Avibactam	+	+	+	+	+	-

Jacoby, N Engl J Med 2005- Shahid, Crit Rev Microbiol 2009 – Livermore, JAC 2010 – Drawz, Clin Microbiol Rev 2010 – Titelman, Diag Microbiol Infect Dis 2011 – Zhanel, Drugs 2013

BETALAKTAMASEINHIBITOREN
Neue BL/BLI-Kombinationen

β-Laktam/β-Laktamase-Inhibitor	Aktivität			
	MRSA	ESBL	Serin-Carbapenemasen (Typ KPC und Oxa-48)	Metallo-β-Laktamase (Carbapenemasen, z. B. NDM, VIM)
Ceftolozan/Tazobactam	–	+	–	–
Ceftazidim/Avibactam	–	+	+	–
Ceftarolin/Avibactam	+	+	+	–
Aztreonam/Avibactam	–	+	+	+
Imipenem/Relebactam	–	+	+	–
Meropenem/RPX7009	–	+	+	–

Aztreonam wird von Metallo-β-Laktamasen nicht gespalten, hat jedoch nur eine mäßige bzw. unzureichende Aktivität gegenüber *Pseudomonas aeruginosa* bzw. *Acinetobacter baumannii*.

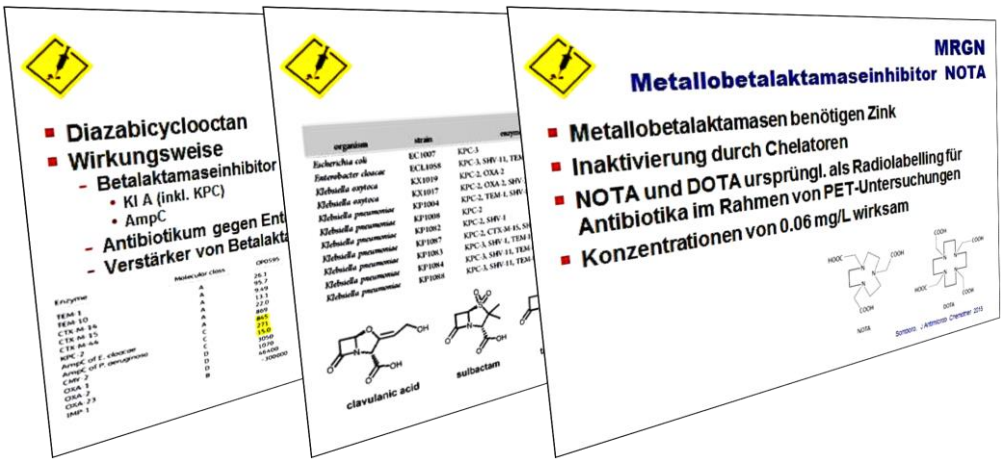
Kern, Internist 2015

BETALAKTAMASEINHIBITOREN
Betalaktamasenkombinationen

Agent	Good Coverage	Poor Coverage
Ceftolozane/ tazobactam	MDR gram negative bacilli, including: **MDR *Pseudomonas*** ESBLs Amp-C producing *enterobacteraciae*	**CRE (and KPC)** MSSA/MRSA *Enterococcus*
Ceftazidime/ avibactam	Gram negatives, including: **CRE (and KPC)** ESBLs *Pseudomonas* Amp-C producing *enterobacteraciae*	MSSA/MRSA *Enterococcus*
Ceftaroline/ avibactam	Gram positive, including MRSA **CRE (and KPC)** ESBLs Amp-C producing *enterobacteraciae*	***Pseudomonas*** ***Acinetobacter***

Castanheira, Antimicrob Agents Chemother 2012 – Zhanel, Drugs 2014 – Lagace-Wiens, Core Evidence 2014

BETALAKTAMASEINHIBITOREN
Was bringt die Zukunft?



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