

# M R G N


SPANNENDE THERAPIEPTIONEN SIND IM KOMMEN



**P I C K I A N T H A L M A N N I K**  
 MELNIGERHEITEN FÜR ANFÄHRLICHE  
 UNIVERSITÄT WÜRZBURG  
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[www.klinik.uni-wuerzburg.de](http://www.klinik.uni-wuerzburg.de)

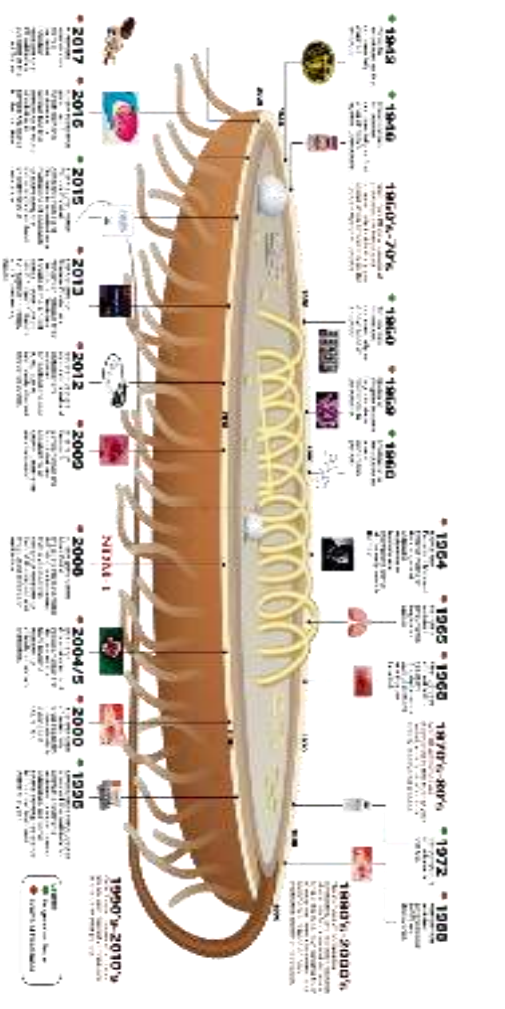



www.66millionsdimpatients.org/wp-content/uploads/2015/03/hygiene-des-soins-des-malins-medecine.jpg 23.11.2017 13:35



## MRGN – SPANNENDE THERAPIEPTIONEN

### Resistenzentwicklung



- 1943 • 1946 • 1949 • 1950 • 1951 • 1952 • 1953 • 1954 • 1955 • 1956 • 1957 • 1958 • 1959 • 1960 • 1961 • 1962 • 1963 • 1964 • 1965 • 1966 • 1967 • 1968 • 1969 • 1970 • 1971 • 1972 • 1973 • 1974 • 1975 • 1976 • 1977 • 1978 • 1979 • 1980 • 1981 • 1982 • 1983 • 1984 • 1985 • 1986 • 1987 • 1988 • 1989 • 1990 • 1991 • 1992 • 1993 • 1994 • 1995 • 1996 • 1997 • 1998 • 1999 • 2000 • 2001 • 2002 • 2003 • 2004 • 2005 • 2006 • 2007 • 2008 • 2009 • 2010 • 2011 • 2012 • 2013 • 2014 • 2015 • 2016 • 2017

- 1984 • 1985 • 1986 • 1987 • 1988 • 1989 • 1990 • 1991 • 1992 • 1993 • 1994 • 1995 • 1996 • 1997 • 1998 • 1999 • 2000 • 2001 • 2002 • 2003 • 2004 • 2005 • 2006 • 2007 • 2008 • 2009 • 2010 • 2011 • 2012 • 2013 • 2014 • 2015 • 2016 • 2017

IDSA 2017, Faces of Antimicrobial Resistance



# MRGN – SPANNENDE THERAPIEOPTIONEN Unsere Sorgenkinder

## GRAM-POSITIVE ERREGER

- **Staphylokokken**
  - MRSA
  - MRSE
  - GISA (Glykopeptid intermediär)
  - LRS (Linezolid-resistente)
- **Enterokokken**
  - VRE (Vancomycin resistente)
  - LRE
- **Clostridium difficile**

## GRAM-NEGATIVE ERREGER

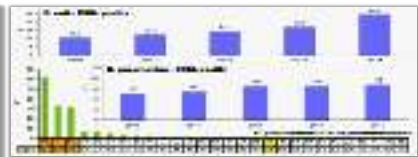
- **Acinetobacter baumannii**
  - 4MRGN
- **Escherichia coli**
  - 3MRGN – ESBL
- **Klebsiella pneumoniae**
  - 3MRGN – ESBL
  - 4MRGN – KPC (NDM-1)
- **Pseudomonas aeruginosa**
  - 4MRGN

## PILZE

- **Candida**
  - Candida auris



# MRGN – SPANNENDE THERAPIEOPTIONEN MRGN in Österreich und Europa



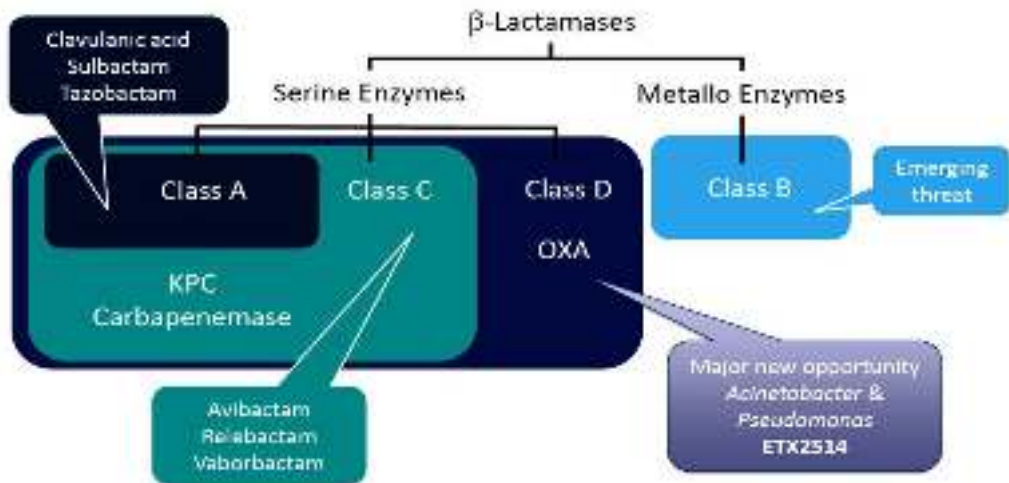
Klassifizierung multiresistenter gramnegativer Erreger auf Basis ihrer phenotypischen Resistenzprofile						
Artenfamiliegruppe	Antibiotikase	β-Lactamase	β-Lactamase	β-Lactamase	β-Lactamase	β-Lactamase
Acinetobacter baumannii	Piperacillin / Tazobactam	R	R	R	R	R
Escherichia coli	Cefepime / ceftazidim / ceftioctam / ceftazidim / ceftioctam	R	R	R	R	R
Klebsiella pneumoniae	Imipenem / meropenem / meropenem	R	R	R	R	R
Pseudomonas aeruginosa	Carbapenem	R	R	R	R	R

Livmore, CID 2002 – Hawkey, AAC 2008 – Hawkey, JAC 2009 – Bush, AAC 2010 – Olivares, Front Microbiol 2013 – AURES 2014  
Rossolini, Integrated symposium IS08, 25th ECCMID 2015 – Forstner, Anästhesiol Intensivmed Notfallmed Schmerzther 2016 – ECDC 2017



# MRGN – SPANNENDE THERAPIEOPTIONEN

## Einteilung der Betalaktamase



Durand-Réville, 253rd ACS National Meeting 2017

www.ambler.com 01.02.2017 14:08



# MRGN – SPANNENDE THERAPIEOPTIONEN

## Erreger & Resistenzmechanismen

Type of $\beta$ -Lactamase	Classic microorganisms or types
Extended-spectrum $\beta$ -Lactamases	<i>Escherichia coli</i> <i>Klebsiella species</i> <i>Proteus species</i>
AmpC	<i>Serratia species</i> <i>Pseudomonas aeruginosa</i> Indole + <i>Proteus</i> <i>Citrobacter species</i> <i>Enterobacter species</i>
Carbapenemases	KPC (Ambler Class A) IMP (Ambler Class B) OXA-type (Class D)

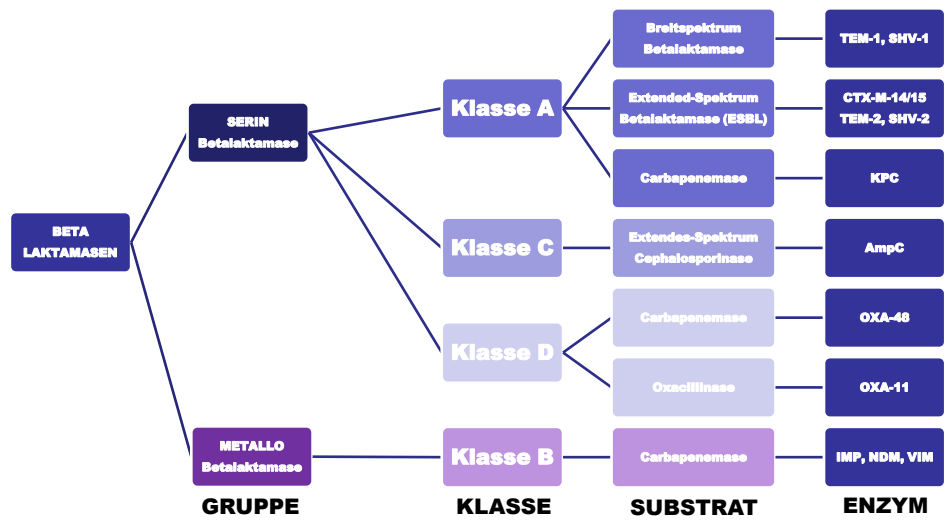
Ambler-Klassifikation	Resistenzmechanismus	<i>Klebsiella pneumoniae</i>	<i>Escherichia coli</i>	<i>Enterobacter cloacae</i>	<i>Enterobacter aerogenes</i>
Klasse A	ESBL (CTXM, TEM, SHV) in Kombination mit Porinlux	+++	+	+	(+)
Klasse B (Metallo-Beta-Laktamase, MBLs)	NDM SIM IMP	+	+	+	(+)
Klasse C	AmpC (FOX, DHA, CMY, MCR, VAI) in Kombination mit Porinlux	+	+	+++	+++
Klasse D (OXA-Besitzer)	OXA-48	+++	++	+	(+)

+++ häufigste Resistenz, +++ zunehmende Resistenz, ++ selten aber regelmäßige Resistenz, (+) Beispiele



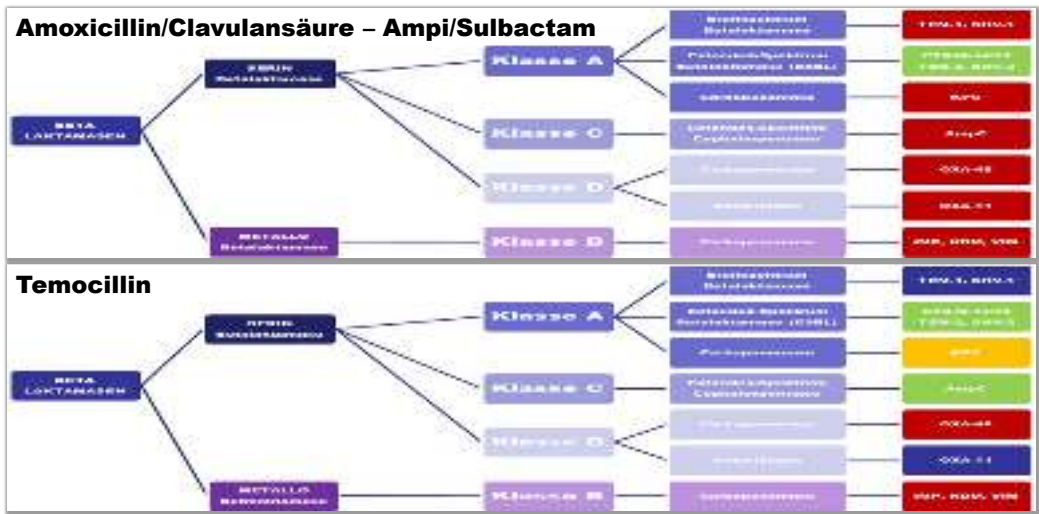
# MRGN – SPANNENDE THERAPIEOPTIONEN

## Unterteilung der Betalaktamase



# MRGN – SPANNENDE THERAPIEOPTIONEN

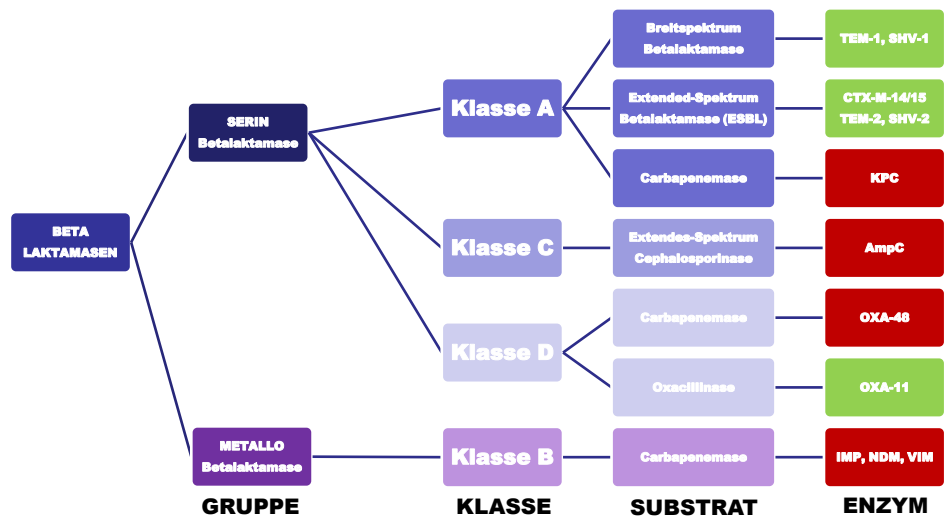
## Amoxi/Clav – Ampi/Sulb & Temocillin



Balakrishnan, J Antimicrob Chemother 2011 – Forstner, Krankenhaushygiene up2date 2014 | Laterre, J Antimicrob Chemother 2014



# MRGN – SPANNENDE THERAPIEOPTIONEN Cefoxitin



# MRGN – SPANNENDE THERAPIEOPTIONEN Avibactam bis Vaborbactam

O=C(O)C1=NC(=O)NC(=O)N1  
 Clevulansäure

O=C(O)C1=NC(=O)N(C2=CC=CC=C2)C(=O)N1  
 Tazobactam

O=C(O)C1=NC(=O)N(C2=CC=CC=C2)C(=O)N1  
 Sulbactam

O=C(O)C1=NC(=O)N(C2=CC=CC=C2)C(=O)N1  
 Avibactam

O=C(O)C1=NC(=O)N(C2=CC=CC=C2)C(=O)N1  
 Vaborbactam

O=C(O)C1=NC(=O)N(C2=CC=CC=C2)C(=O)N1  
 Aztreonam

Klasse 1/A

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

		Clevulansäure	Tazobactam	Avibactam
<b>Class A</b>	TEM, SHV	✓	✓	✓
	CTX-M	✓	✓	✓
	KPC	✗	✗	✓
	KPC	✗	✗	✓
<b>Class B</b>	IMP, NDM, VIM	✗	✗	✗
	Carbapenemase AmpC	✗	✗	✓
	Carbapenemase AmpC	✗	✗	✓
	Carbapenemase AmpC	✗	✗	✓
<b>Class C</b>	ESBL	✗	✗	✓
	ESBL	✗	✗	✓
	ESBL	✗	✗	✓
	ESBL	✗	✗	✓
<b>Class D</b>	OXA-1, -31, -10, -11	✓	✓	✓
	OXA-1, -18	✓	✓	✓
	OXA-23, -10, -48, -58	✓	✓	✓
	OXA-23, -10, -48, -58	✓	✓	✓

Lagacé-Wiens, Core Evid 2014 – Wright, Trends Microbiol 2016



# MRGN – SPANNENDE THERAPIEOPTIONEN Avibactam

- **Differenzierung zu anderen BLI**
  - keine  $\beta$ -Laktam-Struktur
  - Wiederherstellung der Aktivität von Ceftazidim und anderen Betalaktam-Antibiotika gegen KI A, KI C und einige KI D Betalaktamaseinhibitoren
  - keine Induktion von Betalaktamasen
  - 50% niedrigere Wirkkonzentration notwendig
- Zahl der Moleküle ( $t_n$ ), die bis zu einer irreversiblen Hemmung der Betalaktamase verbraucht werden.

	AVIBACTAM	CEFTAZIDIM	CEFTAZIDIM + AVIBACTAM
CEFTAZIDIM	25	1000	400
AVIBACTAM	50	500	100
AVIBACTAM + CEFTAZIDIM	1,25	5	1,25
AVIBACTAM + AVIBACTAM	5	1	50
AVIBACTAM + AVIBACTAM	100	1000	5000
AVIBACTAM + AVIBACTAM	5	1	5
AVIBACTAM + AVIBACTAM	50	1000	5000
AVIBACTAM + AVIBACTAM	100	1000000	1000
AVIBACTAM + AVIBACTAM	1000	10000000	1000

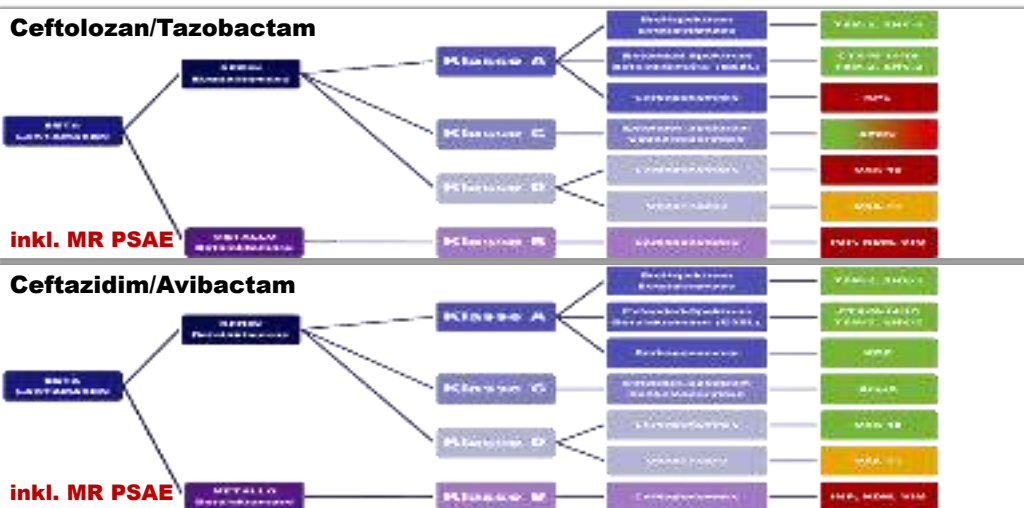
## Avibactam

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

Stachyra, Antimicrob Agents Chemother 2009 – Drawz, Clin Microbiol Rev 2010 – Coleman, Curr Opin Microbiol 2011 – Zhanel, Drugs 2013  
Lahiri, Antimicrob Agents Chemother 2013 – Toussaint, Ann Pharmacother 2014



# MRGN – SPANNENDE THERAPIEOPTIONEN Cefto/Taz & Cefta/Avi





# MRGN – SPANNENDE THERAPIEOPTIONEN Cefto/Taz & Cefta/Avi

**RISIKO**

- Antibiotikaresistenz (Ceftazidim + β-Laktamase Inhibitor) Variante 2 (1)

**WIRKMECHANISMUS**

- aktive Lipidtransfer
- aktiviert die transpeptidase
- aktiviert periplärischen Organismus mit Mutationen ohne Nachbarn

**IN VIVO AKTIVITÄT**

- gegen Gram-positive Bakterien
- gegen Gram-negative Bakterien
- gegen anaerobe Bakterien

**IN VIVO AKTIVITÄT**

- gegen Gram-positive Bakterien
- gegen Gram-negative Bakterien
- gegen anaerobe Bakterien

**PHARMAKOKINETIK**

- Exzellente PK
- gute Tissuepenetration
- minimale Akkumulation
- aktive renale Excretion
- minimale Proteinbindung

**Resistenzmechanismen**

- Phosphotransferase
- β-Lactamase
- Effluxpumpen

**STAPHYLOKOKKEN-LÜCKE II**

**Staphylokokken-Lücke II**

**RECAPTURE T & Z**

Pharmakokinetik

Exzellente PK

gute Tissuepenetration

minimale Akkumulation

aktive renale Excretion

minimale Proteinbindung

**RECAPTURE T & Z**

Pharmakokinetik

Exzellente PK

gute Tissuepenetration

minimale Akkumulation

aktive renale Excretion

minimale Proteinbindung

**RECAPTURE T & Z**

Pharmakokinetik

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**RECAPTURE T & Z**

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Exzellente PK

gute Tissuepenetration

minimale Akkumulation

aktive renale Excretion

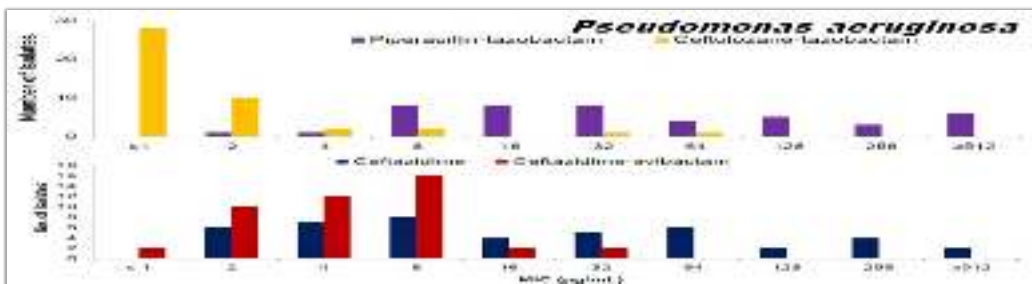
minimale Proteinbindung

**STAPHYLOKOKKEN-LÜCKE II**

Zhanel, Drugs 2014 – Wagenlehner, Lancet 2015 – Krause, Arzneimittelprofil 2017



# MRGN – SPANNENDE THERAPIEOPTIONEN Cefto/Taz & Cefta/Avi



Bacterial group (n)	C/T MIC Range μg/ml	C/T MIC <sub>50</sub>	C/T % Sus	CZA MIC Range μg/ml	CZA MIC <sub>50</sub>	CZA % Sus
<i>Pseudomonas aeruginosa</i> (45)	0.25-16	8	87	0.5-64	16	82
BLR <i>P. aeruginosa</i> (10)	2-16	8	60	2-64	64	50
<i>Enterobacteriaceae</i> (75)	0.125-256	32	96	0.032-32	2	99
<i>Enterobacter</i> spp. (17)	0.5-64	64	18	0.125-32	4	94
<i>Escherichia coli</i> (29)	0.125-4	0.5	97	0.032-2	0.5	100
<i>Acinetobacter baumannii</i> (24)	0.25-256	128	42	0.125-8	2	100
ESBL <i>A. baumannii</i> (8)	0.25-4	4	88	0.125-1	1	100
CRE <i>A. baumannii</i> (16)	1-256	>256	19	1-8	4	100

Shields, ICAAC 2015 – Gonzalez, Ann Lab Med 2017



## MRGN – SPANNENDE THERAPIEOPTIONEN Cefto/Taz & Cefta/Avi

1. *Pseudomonas aeruginosa* 4 MRGN nachlich  
Aufmerksamkeit gramnegative Stäbchen (MRGN) mit Resistenzfaktoren: Empfindlichkeit gegen 4 von 4 Antibiotikagruppen (Aminoglykoside/Ame, Cephalosporine der 3./4. Generation, Carbapeneme, Flavonolactone)
2. *Enterococcus faecium* nachlich
3. *Cardiobacterium* massig

Antibiogramm	Keim 1	Keim 2
Amoxicillin		-
Piperacillin	-	
Piperacillin/Tazobactam	-	
Cefepim	-	
Ceftazidim/Avibactam	-	
Ceftazidim	-	
Ceftioctam/Netilmicin	-	
Imipenem	-	
Meropenem	-	

Antibiogramm	Keim 1	Keim 2
Aztreonam	-	
Ciprofloxacin	-	
Amikacin	+	
Genfermin	+	
Tobramycin	+	
Isoszlamin		+
Wancamycin		+
Colistin	+	
Linezolid		+

+ = sensible, ++ = Intermediate, - = resistent, N = nicht inhibiert [ ] minimale Hemmkonzentration in mg/l

**STAPHYLOKOKKEN-LÜCKE !!**

AKH Wien 2017



## MRGN – SPANNENDE THERAPIEOPTIONEN Ceftazidim/Avibactam

### Combinations of avibactam and carbapenems exhibit enhanced potencies against drug-resistant *Mycobacterium abscessus*.

**AIM:** The objective of this study was to assess if avibactam, a new  $\beta$ -lactamase inhibitor, can restore the potency of carbapenems, a subclass of  $\beta$ -lactams, against *Mycobacterium abscessus* clinical isolates.

**MATERIALS & METHODS:** 25 *M. abscessus* clinical isolates that are resistant to multiple drugs currently used to treat its infection were included. MIC of carbapenems alone and in combination with avibactam against these strains were determined.

**RESULTS:** Telaprepem, an oral carbapenem, and erapipenem and panipipenem exhibited the greatest shift in MIC when supplemented with avibactam.

**CONCLUSION:** Avibactam restores MICs of telaprepem, erapipenem and panipipenem against *M. abscessus* to therapeutically achievable concentrations and raises the possibility of usefulness of these carbapenems to treat drug-resistant *M. abscessus* infections.

### In Vitro Discordance with In Vivo Activity: Humanized Exposures of Ceftazidime-Avibactam, Aztreonam, and Tigecycline Alone and in Combination against New Delhi Metallo- $\beta$ -Lactamase-Producing *Klebsiella pneumoniae* in a Murine Lung Infection Model.

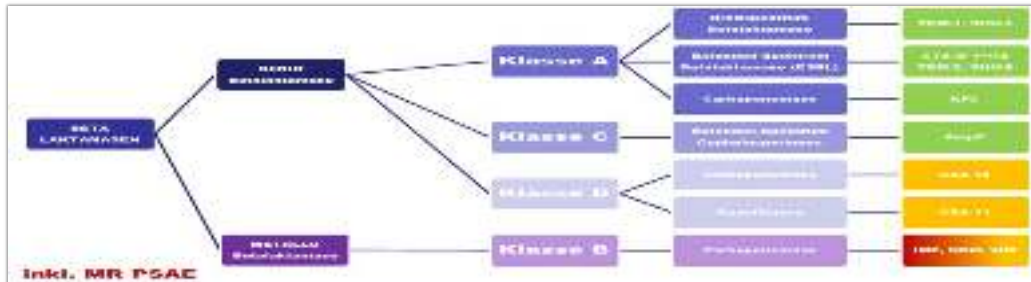
The management of infections with New Delhi Metallo-beta-lactamase-1 (NDM1) producing bacteria remains clinically challenging given the multi-drug resistant (MDR) phenotype associated with these bacteria. Despite resistance *in vitro*, ceftazidime-avibactam previously demonstrated *in vivo* activity against NDM1 Enterobacteriaceae. Herein, we observed *in vivo* synergy with ceftazidime-avibactam and aztreonam against a MDR *K. pneumoniae* harboring NDM1. *In vivo*, humanized doses of ceftazidime-avibactam monotherapy resulted in  $> 2$  log<sub>10</sub>CFU bacterial reduction; therefore, *in vivo* synergy was observed.

Kaushik, Future Microbiol 2017 – Monogue, Antimicrob Agents Chemother 2017





## MRGN – SPANNENDE THERAPIEOPTIONEN Meropenem/Vaborbactam



### FDA Approves Unique Antibiotic Combo Drug Vabomere

Vabomere is a combination antibiotic that includes meropenem, a penem antibacterium, and vaborbactam, a non-suicidal beta-lactamase inhibitor. Meropenem inhibits cell wall synthesis and vaborbactam protects meropenem from degradation by specific serine beta-lactamases; it has no antibacterial activity.



MPR 30.08.2017



## MRGN – SPANNENDE THERAPIEOPTIONEN Meropenem/Vaborbactam

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

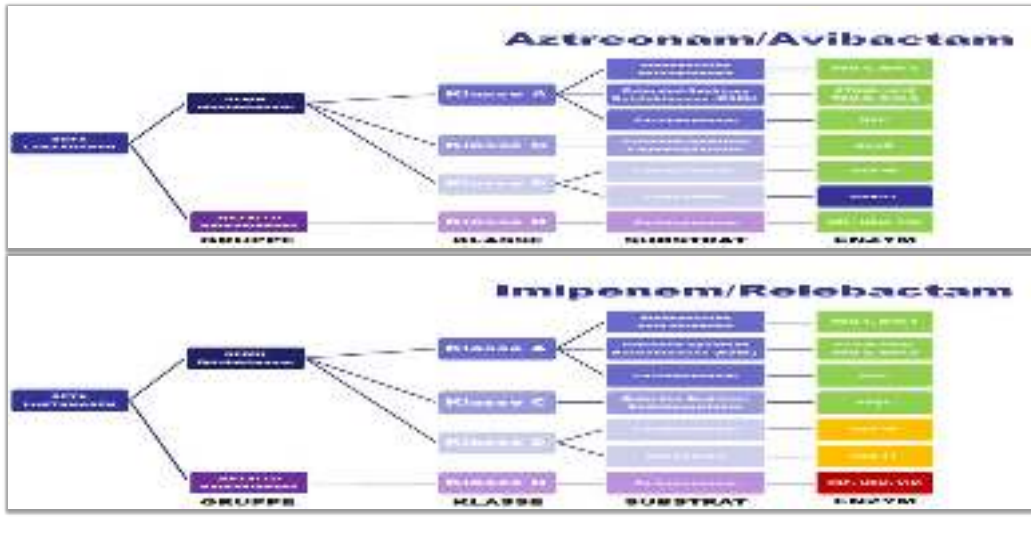
Spectrum	Beta-laktamase Inhibitor			
	Ticarcillin	Azobactam	Meropenem	Vaborbactam
Class A ESBLs	+	+	+	+
Class A carbapenemase (KPC)			+	+
Class B ESBLs				
Some class C enzymes	+	+	+	+
Most class II enzymes			+	+

P. Aeruginosa (n=98)	MIC <sub>50</sub> (µg/ml)	MIC <sub>90</sub> (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 – Drawz, Rev Clin Microbiol Rev 2010 – Page, Ann NY Acad Sci 2013  
Lapuebla, Antimicrob Agents Chemother 2015 – Toussaint, Ann Pharmacother 2015 – Chellat, Angew Chemie 2016

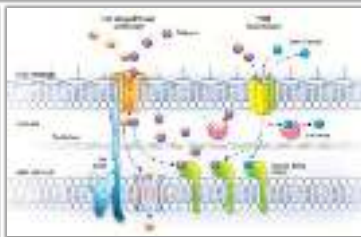
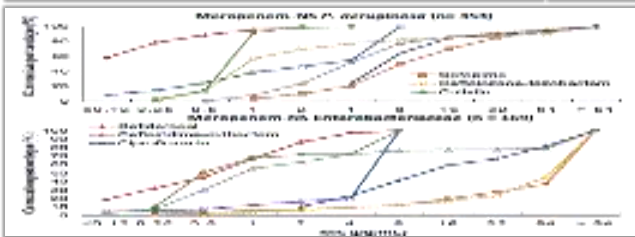
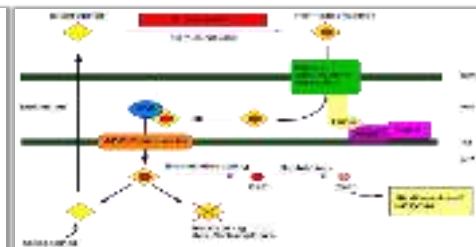


# MRGN – SPANNENDE THERAPIEOPTIONEN Avibactam & Relebactam



# MRGN – SPANNENDE THERAPIEOPTIONEN Cefiderocol

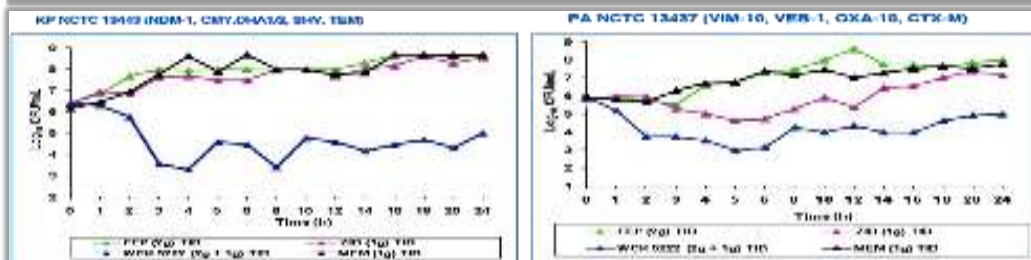
- Siderophore sind Moleküle, die Eisenionen komplexieren
- Eisen für Bakterien essentiell für lebensnotwendige zelluläre Prozesse
- Siderophor-Sulfactam-Konjugat, abgeleitet von Tigemonam, transportiert den AB-Fe<sup>3+</sup>-Komplex aktiv durch die äußere Bakterienmembran
- Hemmung von PBP1a, PBP2a und PRP3 innerhalb der Bakterienzelle
- Inhibitor der Klasse C Betaaktamazen





## MRGN – SPANNENDE THERAPIEOPTIONEN Cefepim/Zidebactam

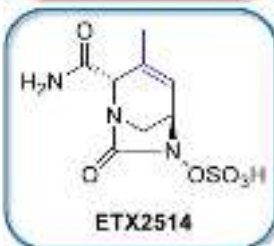
- ESBL Gram-negative Enterobakterien
  - inkl Piperacillin-Tazobactam resistente Stämme
- Cefepim-res Enterobacter mit CMY  $\beta$ -Laktamase
- KPC und andere CRE mit OXA 48/181  $\beta$ -Laktamase
- MBL/NDM Enterobakterien und Pseudomonaden
- Ceftazidim und Meropenem res Pseudomonaden
- Imipenem resistenter Acinetobacter
- Staphylokokken, Pneumokokken & Streptokokken



Moya, ID week 2016



## MRGN – SPANNENDE THERAPIEOPTIONEN Diazabicyclooctanon ETX2514



### Betalaktamasehemmung Avibactam vs ETX2514

Compos	Dosis	Class A				Class C			Class D			
		T144	OT44P	SP2	Q20	Abom (P)	Ami (A)	OXA1	OXA2	Ime (P)	MILP	
avibactam		4 x 12	2 x 12	5 x 12	1 x 12	0 x 12	2 x 12	7 x 12	1 x 12	5 x 12	8 x 12	
ETX2514		1 x 12	1 x 12	1 x 12	1 x 12	0 x 12	1 x 12	0 x 12	1 x 12	0 x 12	1 x 12	
1-diazabicyclooctanon		100	80	100	80	200	200	100	80	100	100	

Tommasi, ECCMID 2017



The image shows two overlapping smartphone screens displaying the 'Antibiotika & Antiinfektiva' app. The background screen shows a home screen with a yellow background and several icons: a registered trademark symbol (R), a hexagonal chemical structure, a microscope, a biohazard symbol, and a pill. The foreground screen shows a search menu with the following options: 'Gesamtsuche', 'Handelsnamen', 'Wirkstoffe', 'Bakterien', 'Indikationen', 'Nebenwirkungen', 'Minos', 'Pflanzl.', and 'Pflanzl.'. At the bottom of the menu, it says 'Weiterführende Informationen'.



**ERHÄTLICH**  
Google Play Store

**ERHÄTLICH**  
im App Store

[www.antibiotika-app.eu](http://www.antibiotika-app.eu)