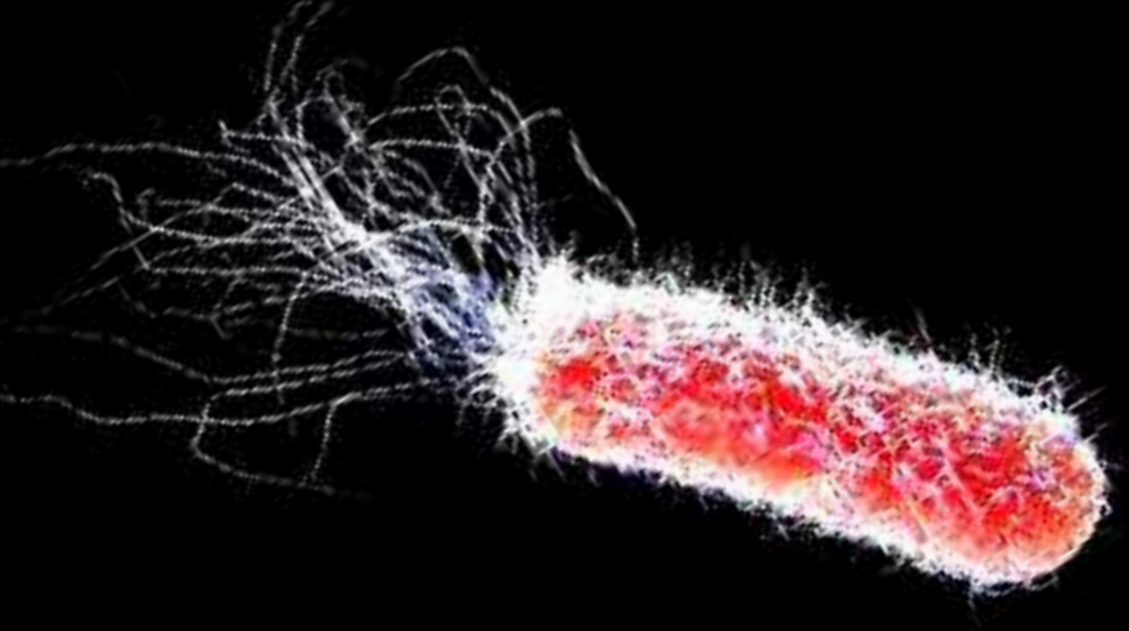
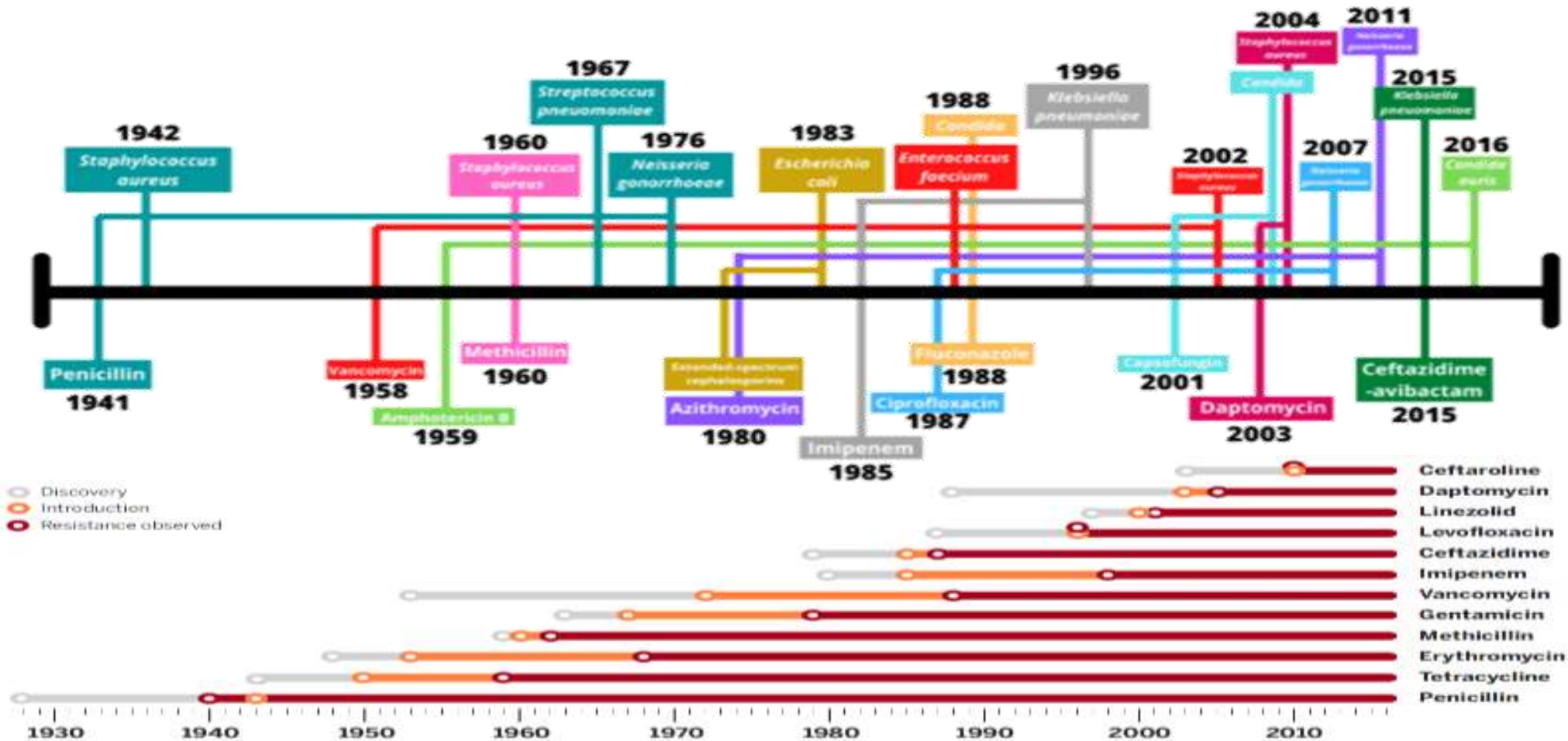


NEUE ANTIBIOTIKA

FLORIAN THALHAMMER
FACHARZT FÜR INNERE MEDIZIN & INFEKTIOLOGIE/TROPENMEDIZIN
UNIVERSITÄTSKLINIK FÜR UROLOGIE – UNIVERSITÄTSKLINIKUM & MEDIZINISCHE UNIVERSITÄT WIEN
www.antibiotika-app.eu – florian.thalhammer@meduniwien.ac.at

www.caracteristicass.de/escherichia-coli/ 21.04.2019 20:43

NEUE ANTIBIOTIKA
Entdeckung – Einführung – Resistenz

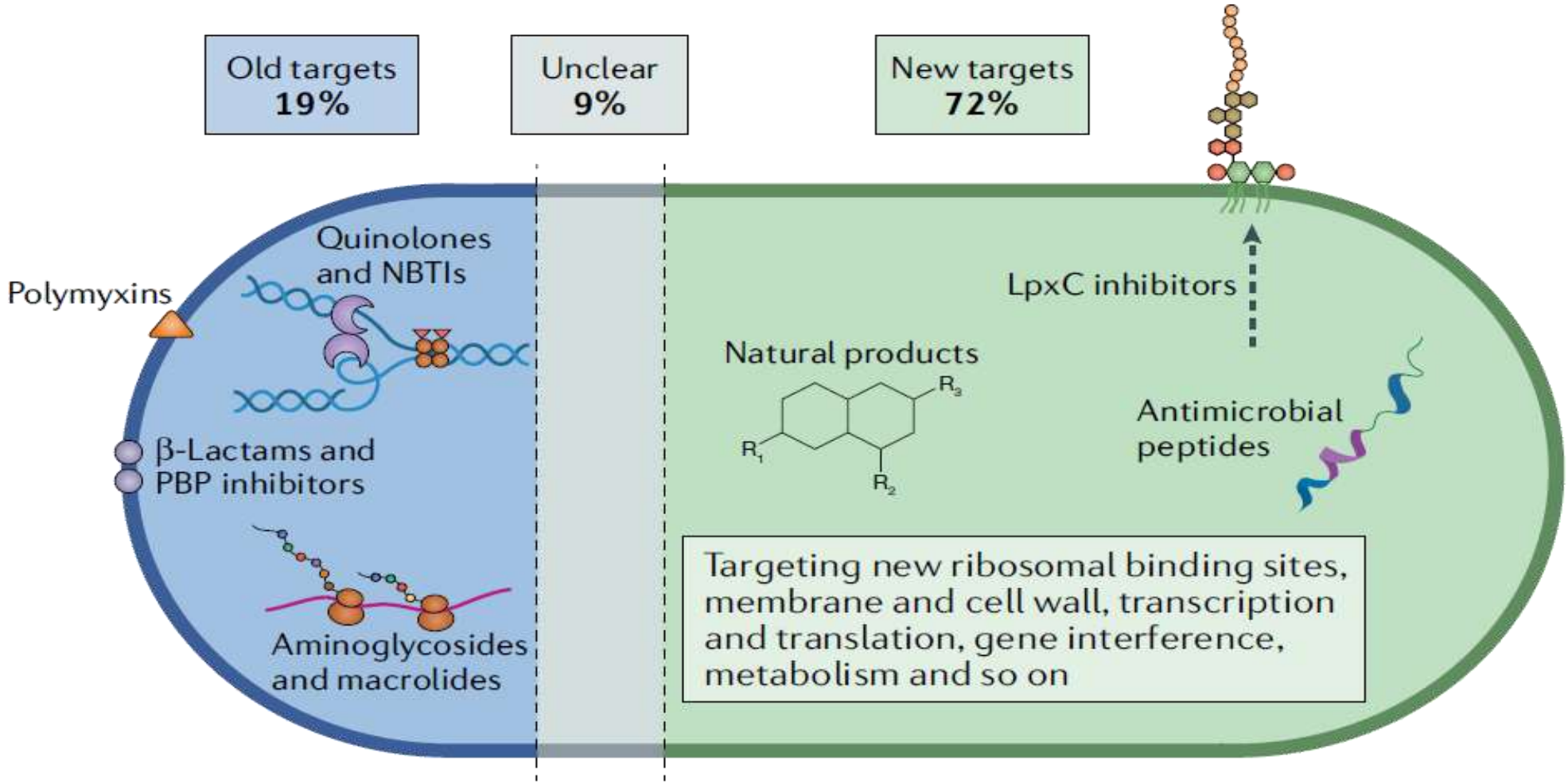


Kupferschmidt, Science 2021 – www.lgcstandards.com/DE/de/Resources/Blogs/Antibiotic_resistance 2021_10_06

NEUE ANTIBIOTIKA
ESCKAPE

Schwerdtner, Urologe 2020

NEUE ANTIBIOTIKA
Zukunft



Theuretzbacher, Nat Rev Microbiol 2020

NEUE ANTIBIOTIKA
Antibiotikagruppen in klin Pipeline

- β-lactam + BLI ..... n=11 (42%)
- Tetracycline ..... n=3 (11%)
- Aminoglycoside..... n=1 (4%)
- Topoisomerase inhibitor ..... n=2 (7%)
- Macrolide/ketolide ..... n=2 (8%)
- Oxazolidinone..... n=1 (4%)
- Polymyxin ..... n=2 (8%)
- Antibiotic hybrid ..... n=2 (8%)
- FabI inhibitor..... n=1 (4%)
- FtsZ inhibitor ..... n=1 (4%)

WHO 2020

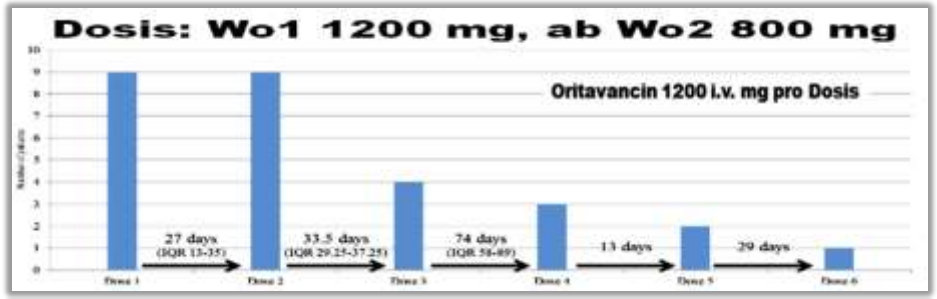
NEUE ANTIBIOTIKA
MSSA & MRSA

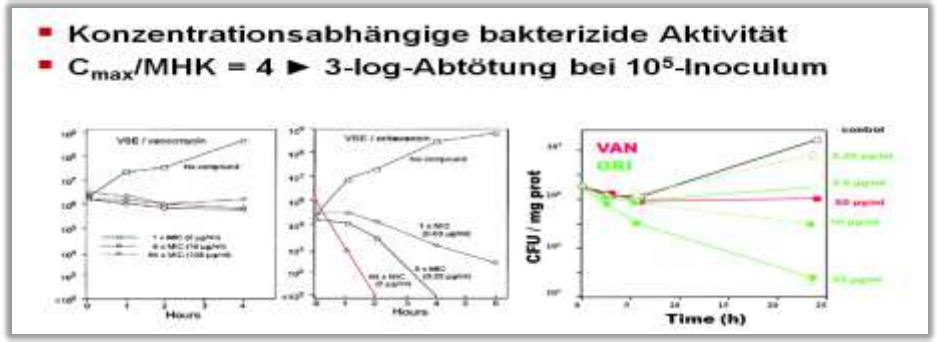
	Cephalosporins	Lipopeptides		Lipoglycopeptides		Oxazolidinones		Fluoroquinolones	Tetracyclines
	Ceftaroline	**Daptomycin**	**Telavancin**	**Dalbavancin**	**Oritavancin**	**Linezolid**	**Tedizolid**	**Delafloxacin**	**Omadacycline**
In vitro activity	MSSA, MRSA, CoNS, streptococci, some *Enterococcus faecalis* isolates	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanA, vanB*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanB*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanB*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanA, vanB*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanA, vanB*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanA, vanB*	MSSA, MRSA, CoNS, streptococci, *E. faecalis*	MSSA, MRSA, CoNS, streptococci, enterococci including VRE *vanA, vanB*
No activity	*Enterococcus faecium*, VRE *vanA, vanB*		VRE *vanA*	VRE *vanA*				*E. faecium*, VRE *vanA, vanB*	
Drug target	Cell wall synthesis	Cell wall synthesis	Cell wall synthesis	Cell wall synthesis	Cell wall synthesis	Protein synthesis	Protein synthesis	DNA replication	Protein synthesis
FDA/EMA approved dosing regimen (for ABSSSI, unless otherwise mentioned)	600 mg b.i.d. IV	ABSSSI 4 mg/kg/day IVBSI/IE 6 mg/kg/day IV	10 mg/kg/day IV	1500 mg IV single doseAlternative: 1000 mg IV single dose at day 1, followed by 500 mg IV single dose at day 8	1200 mg IV single dose	600 mg b.i.d. IV / PO	200 mg q.d. IV / PO	300 mg b.i.d. IV OR450 mg b.i.d. PO	Loading dose: - IV: 200 mg q.d. on day 1 OR 100 mg b.i.d on day 1- PO (for ABSSSI only): 450 mg q.d. on day 1 and 2. Maintenance: - IV: 100 mg q.d. OR- PO: 300 mg q.d.
Recommended dosing regimen for IE and OSM/PJI	600 mg b.i.d. - t.i.d. IV	6-12 mg/kg/day IV	No data	No data	No data	No data	No data	No data	No data

Bloem, J Clin Med 2021

NEUE ANTIBIOTIKA
Oritavancin

- **Dosierung**
  - LD 1.2 g Wo1 i.v.
  - ED 0.8 g ab Wo2 i.v.
- **CAVEAT's**
  - Infusionsdauer 3 Stunden
  - Interaktionen mit Heparin, Marcoumar & Gerinnungtests
- **Indikation**
  - MRGP-Spektrum inkl VRE
  - VRE-Infektionen

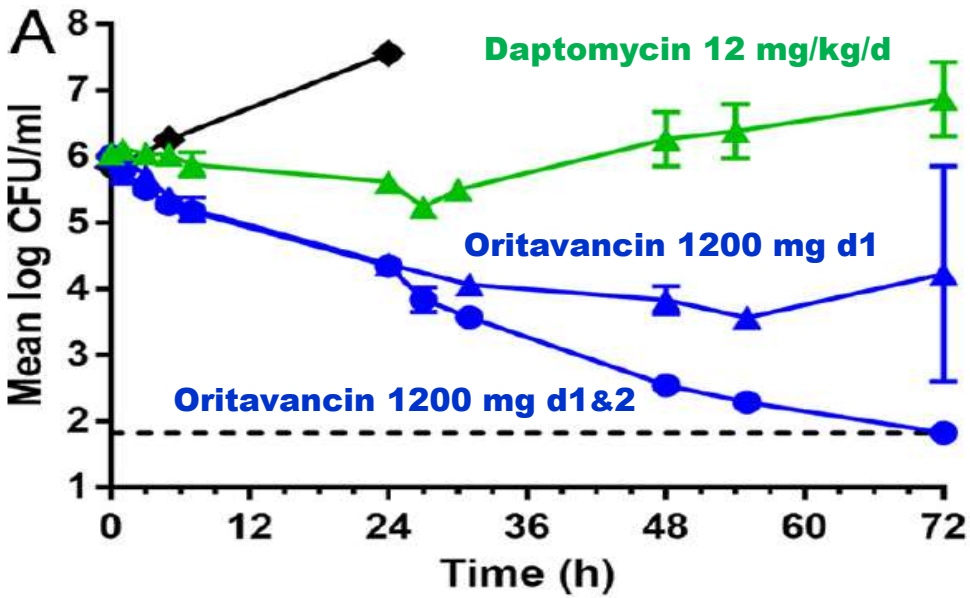


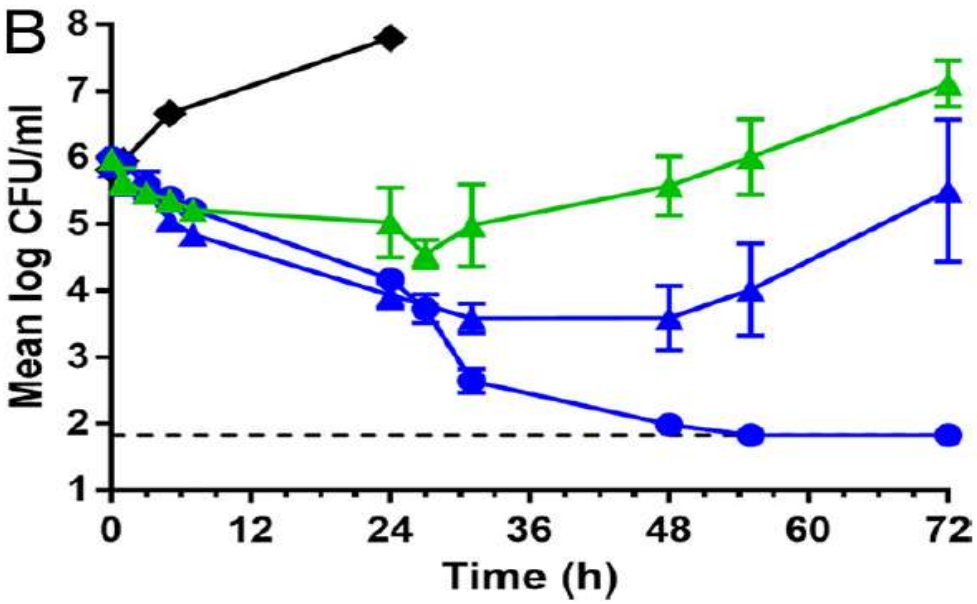


	antibiotic	breakpoint		susceptibility		
		S	R	MIC_{50}	MIC_{90}	range
EUCAST	telavancin	≤ 0.125	> 0.125	0.03	0.06	≤ 0.015 - 0.25
	dalbavancin	≤ 0.125	> 0.125	0.06	0.06	≤ 0.008 - 0.25
	oritavancin	≤ 0.125	> 0.125	0.03	0.03	≤ 0.008 - 0.25
	ceftobiprole	≤ 2	> 2	1	1	0.25 - 2
	ceftaroline	≤ 1	> 1	0.5	1	0.06 - 4
	tedizolid	≤ 0.5	> 0.5	0.25	0.25	0.03 - 0.5
FDA	delafloxacin	≤ 0.25	≥ 1	0.06	0.5	≤ 0.004 - 4

Boucher, N Engl J Med 2014 – Gilchrist, J Antimicrob Chemother 2015 – Thalhammer, Österreichische Ärztezeitung 2016
Tulkens, ECCMID 2018 – Schulz, Pharmacother 2018 – Chastain, Int J Antimicrob Agents 2019

NEUE ANTIBIOTIKA
Oritavancin





	MIC (µg/mL)		
Resistance type	Vancomycin	Teicoplanin	Oritavancin
Van-A	64–1000	16–512	8–16
Van-B	4–1000	0.5–1	8–16
Van-C	2–32	0.5–1	8–16
Van-D	64–128	4–64	
Van-E	8–32	0.5	
Van-G	16	0.5	

DOSIERUNG

2 x 1200 mg Oritavancin innerhalb von 24 Stunden

Zeng, Cold Spring Harb Perspect Med 2016 – Sweeney, J Antimicrob Chemother 2017 – Belley, Antimicrob Agents Chemother 2018

NEUE ANTIBIOTIKA
zugelassen, aber nicht eingeführt

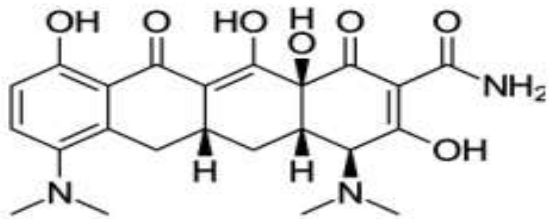
Name (trade name)	Market authorization holder	Approved by (date)	Antibiotic class	Route of administration	Indication/s	WHO EML & AWaRe	Expected activity against priority pathogens				Innovation			
							CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Delafloxacin (Baxdela)	Melinta	FDA (6/2017 ABSSSI, 10/2019 CAP) MAA	Fluoroquinolone	iv & oral	ABSSSI, CAP	AWaRe: Watch	○	○	○	●	-	-	-	-
Vaborbactam + meropenem (Vabomere)	Melinta	FDA (8/2017) EMA (11/2018)	Boronate BLI + carbapenem	iv	cUTI	WHO EML & AWaRe: Reserve	○	○	●[1]	/	?[2]	✓	-	-
Plazomicin (Zemdri)	Achaogen	FDA (8/2018)	Aminoglycoside	iv	cUTI	WHO EML & AWaRe: Reserve	○	○	●	/	-	-	-	-
Eravacycline (Xerava)	Tetraphase	FDA (8/2018) EMA (9/2018)	Tetracycline	iv	cIAI	AWaRe: Reserve	?	○	●	/	-	-	-	-
Omadacycline (Nuzyra)	Paratek	FDA (10/2018)	Tetracycline	iv & oral	CAP (iv), ABSSSI (iv, oral)	AWaRe: Reserve	○	○	○	●	-	-	-	-
Relebactam + imipenem/ cilastatin (Recarbrio)	MSD	FDA (7/2019 cUTI/ cIAI, 7/2020 HAP/ VAP)	DBO-BLI + carbapenem/ degradation inhibitor	iv	cUTI, cIAI, HAP/VAP		○	?	●[1]	/	-	-	-	-
Lefamulin (Xenleta)[5]	Nabriva	FDA (8/2019)	Pleuromutilin	iv & oral	CAP		/	/	/	●	?	✓[3]	-	-
Pretomanid (PA-824)	TB Alliance	FDA (8/2019) EMA (7/2020)	Nitroimidazole	oral	XDR-TB and treatment intolerant or non-responsive MDR-TB		/	/	/	●[4]	-	-	-	-
Lascufloxacin (Lasvic)	Kyorin Pharmaceutical	PMDA (8/2019)	Fluoroquinolone	iv & oral	CAP, otorhinolaryngological		○	○	○	?	-	-	-	-
Cefiderocol (Fetroja)	Shionogi	FDA (11/2019) EMA (4/2020)	Siderophore cephalosporin	iv	cUTI		●	●	●	/	?	-	-	-
Levonadifloxacin (Emrok) Alalevonadifloxacin (Emrok O)	Wockhardt	DCGI (1/2020)	Fluoroquinolone	iv & oral	ABSSSI		○	○	○	●	-	-	-	-

Pathogen activity: ● active; ? possibly active; ○ not or insufficiently active; / activity not assessed, as the antibiotic is focused and developed for only either Gram-positive cocci or Gram-negative rods. The only agents assessed against OPPs were those that are not active against critical priority pathogens. OPP includes the high- and medium-priority pathogens.

WHO 2020

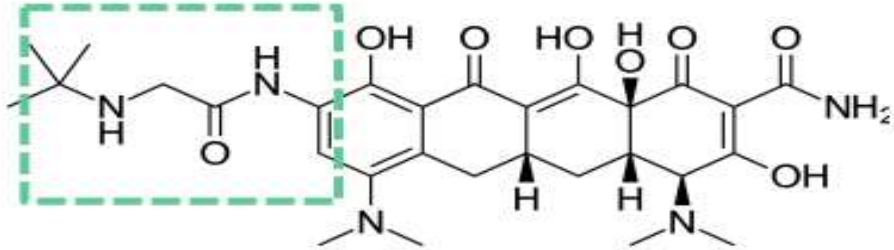
NEUE ANTIBIOTIKA
Eravacyclin – Omadacyclin

minocycline



Limited by resistance

tigecycline



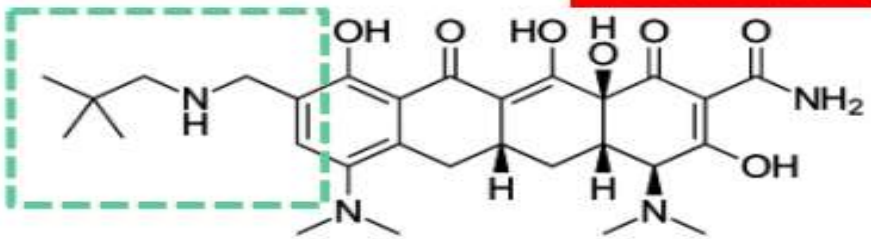
Active against many tetracycline-resistant strains

No pseudomonal activity
IV only
Limited by toxicity

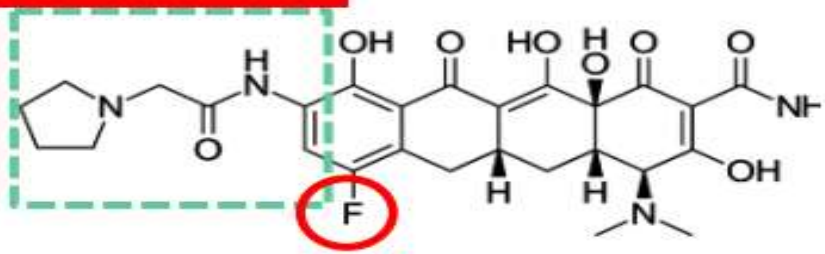
omadacycline

Oral
active on tetracycliines resistant strains

No useful activity against Pseudomonas



eravacycline



NEUE ANTIBIOTIKA
Eravacyclin – Omadacyclin

Eravacyclin – Omadacyclin

- Tetracycline
  - Doxycyclin
  - Minocyclin (Minocin®)
  - Oxytetracyclin
  - Tetracyclin (Mysteclin®)
- Glycylcycline
  - Tigecyclin (Tygacil®)
- Flurocycline
  - Eravacyclin (Xerava®)
  - Omadacyclin (Nuzyra®)

ambulanter w. Pneumonie	1 x 0,3 g p.o.
Akne vulgaris	1 x 0,3 g p.o.
Chlamydieninfektion, Adnexitis	
Lymphogranuloma inguinale	
Brucellose, Leptospirose, Tularämie	
Borreliose, Rickettsiose	
Malaria, Melioidose, Aktinomykose	
Haut- & Weichteilinfektion	1 x 300 mg i.v.
NAP, VAP	
kompl Bauchinfektion	2 x 1 mg/kg iv
Hautinfektionen	1 x 200 mg i.v.
Pneumonie (CAP)	1 x 300 mg po

Eravacyclin

Species (n)	ESBL	bla_{KPC}	bla_{OXA}	Eravacycline MIC_{50}/MIC_{90}	Tigecycline MIC_{50}/MIC_{90}
E. coli (2,866)	13%	0.17%	-	0.12 / 0.5	4 / >16
K. pneumoniae (944)	33%	13%	-	0.25 / 1.0	0.5 / 2.0
Enterobacter aerogenes (90)	22%	3.3%	-	0.25 / 1.0	0.5 / 2.0
Enterobacter cloacae (124)	23%	3.2%	-	0.5 / 1.0	0.5 / 2.0
Acinetobacter baumannii (158)	67%	0.63%	36%	0.5 / 1.0	2.0 / 4.0

Abdallah, Antimicrob Agents Chemother 2015 – Scott, Drugs 2019

Tigecyclin

Gram-positive Bakterien	JA	*E. faecalis*, *S. aureus* (MSSA); *S. agalactiae*. *S. anginosus* grp. (inkl. *S. anginosus*, *S. intermedius*, *S. constellatus*), *S. pyogenes*, *E. avium*, *E. casseliflavus*; *E. gallinarum*, *L. monocytogenes*; *S. epidermidis* (MSSE), *S. haemolyticus*, *E. faecium*
Gram-negative Bakterien	JA	*C. freundii*, *E. cloacae*, *E. coli*, *K. oxytoca*, *K. pneumoniae*, *A. hydrophila*, *C. koseri*, *E. aerogenes*, *P. multocida*, *S. marcescens*
Anaerobier	JA	*B. fragilis*, *B. thetaiotaomicron*, *B. uniformis*, *B. vulgatus*, *C. perfringens*, *P. micros*, *B. distasonis*, *B. ovatus*, *Peptostreptococcus* spp., *Porphyromonas* spp., *Prevotella* spp.
resistente Gram-positive	JA	*S. aureus* (MRSA), *S. epidermidis* (MRSE), *E. faecalis* (VRE), *E. faecium* (VRE)
resistente Gram-negative	JA	*Acinetobacter baumannii*, *S. maltophilia* ESBL-Enterobakterien
P. aeruginosa	NEIN	**Pseudomonas-Lücke schließen !**

Omadacyclin

- **i.v. > p.o.**
  - Tg1 1x 200 mg i.v. über 60 min
  - Tg1 2x 100 mg i.v. über 30 min
  - Tg2 1x 100 mg i.v. über 30 min
  - Tg2 1x 300 mg p.o.
- **p.o.**
  - Tg1&2 1x 450 mg p.o.
  - Tg3 1x 300 mg p.p.

- May need to reduce concomitant anticoagulant dose
- Inj: do not give with multivalent cation-containing solutions (eg, Ca, Mg, Al) through same IV line
- Tabs: after dosing, avoid food or drink (except water) for 2hrs; and avoid dairy, antacids, iron preparations, multivitamins for 4hrs

NEUE ANTIBIOTIKA
Omadacyclin

1325

Activity and Efficacy of Omadacycline against *Clostridium difficile*

Oak Kim,[1] Raina Gay Leahy,[1] Maria Traczewski,[2] Ann Macone,[1] Judith Steenbergen[1]*, S. Ken Tanaka[1]

[1]Paratek Pharmaceuticals, King of Prussia, Pennsylvania, USA; [2]Clinical Microbiology Institute, Wilsonville, Oregon, USA

ABSTRACT

Introduction: Omadacycline (OMC) is a new aminomethylcycline in Phase 3 clinical development for the oral and intravenous treatment of acute bacterial skin and skin structure infections (ABSSSI) and community acquired bacterial pneumonia (CABP). OMC has broad-spectrum activity against Gram-positive, Gram-negative, and atypical bacteria.

Material and methods: OMC was tested *in vitro* against 27 clinical isolates of *C. difficile* (Cd) using both broth microdilution and agar dilution methods according to CLSI guidelines. The efficacy of OMC was determined in the hamster model of CDAD (ViviSource Laboratories, Inc., Waltham MA). Male LGV-Golden Syrian Hamsters were pretreated with a subcutaneous (SC) dose of clindamycin (10 mg/kg) and infected 24 hours later by oral gavage with a suspension of a 48 hour culture of Cd ATCC 43596, resulting in an inoculum of approximately 1.3×10^7 CFU/hamster. At 24 hours post infection, animals were treated PO with OMC (50 mg/kg/day), vancomycin (VAN 50 mg/kg/day) or vehicle for 5 days.

Results: The MIC_{90} for OMC against Cd was 0.06 mg/L by broth dilution and 0.12 mg/L by agar dilution, and OMC was more active than doxycycline (MIC_{90} = 0.5 mg/L by broth and 1 mg/L by agar). Against the infection model strain, OMC was as active as tigecycline, metronidazole, and VAN (MIC = 0.06 mg/L for all drugs). Day 2 post infection, 100% of OMC treated animals were alive, compared to 40% and 0% for VAN and vehicle control animals. For the OMC-treated animals, survival declined to 60% by Day 3 and remained at 60% until declining to 40% on Day 13 and to 0% by Day 16. Animals treated with VAN that survived the initial 2 days began to die by Day 11 (30% survival) and all animals succumbed to infection by Day 14. Overall, the median survival for OMC treated animals was 12 days compared to 2 days for VAN.

Conclusion: OMC exhibited potent *in vitro* activity against *C. difficile* and efficacy in the hamster model of CDAD and might offer potential for the treatment of *C. difficile* infections.

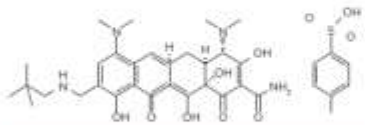
INTRODUCTION

C. difficile is the leading cause of healthcare-associated diarrhea and the most frequent cause of mortality associated with gastroenteritis in the healthcare system (Johanesen et al, 2015; Cohen et al, 2010). A recent surveillance study reported an estimated 450,000 infections and 29,000 deaths from *C. difficile* in the United States in 2011 (Lessa et al, 2015). Costs associated with *C. difficile* infection were estimated at $4.8 billion annually (Lessa et al, 2015). Treatment guidelines recommend a proactive approach to prevention as well as diagnosis and management of *C. difficile* infection (Cohen et al, 2010; Debast et al, 2014).

Most antibiotics have been implicated as a cause of *C. difficile* infections, although the risk with tetracyclines is among the lowest of antibiotic classes (Deshpande et al, 2013). Some evidence suggests that the tetracycline, doxycycline, may have protective effects against development of *C. difficile* infection (Turner et al, 2014).

Omadacycline is a first in class aminomethylcycline (Honeyman et al, 2015; **Figure 1**). Omadacycline exhibits a broad-spectrum of *in vitro* microbiological activity including Gram-positive and Gram-negative aerobes, anaerobes, and atypical bacteria (Macone et al, 2014; Flamm et al, 2015a, b, c; Dubois et al, 2015). Omadacycline has a half-life of approximately 17 hours after oral and IV administration, reaches peak plasma concentrations of 0.6 mg/L after oral administration, and exhibits low protein binding (21%). In earlier clinical studies, omadacycline was comparable to linezolid for treating patients with complicated skin infection. Phase 3 clinical development is ongoing with omadacycline as oral and intravenous (IV) monotherapy for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community acquired bacterial pneumonia (CABP). This study evaluated the microbiological activity of omadacycline *in vitro* against clinical isolates of *C. difficile* and determined efficacy in a hamster model of *C. difficile*.

Figure 1. Chemical Structure of Omadacycline



MATERIALS AND METHODS

In Vitro Activity

- Omadacycline was tested *in vitro* against 27 clinical isolates of *C. difficile* using broth and agar microdilution methods according to CLSI guidelines.
- Disks containing omadacycline 15 or 30 mcg were prepared.
- 96-well plates were filled with Wilkins-Chalgren broth containing final concentrations of 16 to 0.016 mg/L of each test compound.
- Plates were incubated for 48 hours under anaerobic conditions.
- Each test was run in duplicate.

Efficacy in Hamster Model of *C. difficile*

- The efficacy of omadacycline was determined in the hamster model of *C. difficile*-associated diarrhea (ViviSource Laboratories, Inc., Waltham MA).
- Male LGV-Golden Syrian Hamsters (Charles River Laboratories Inc., Wilmington, MA) weighing 80-100 g were used.
  - Hamsters were kept in a room maintained at 64-76° F (17.8-24.4° C) with humidity set at 40%-70%, and standard rodent diet and water were available *ad libitum*.
- Hamsters were pretreated with a subcutaneous (SC) dose of clindamycin (10 mg/kg) 24 hours prior to injection.
- *C. difficile* ATCC 43596 was obtained from American Type Culture Collection, Manassas, VA.
- *C. difficile* ATCC 43596 was cultured from freezer stocks under anaerobic conditions on Brucella agar with 5% sheep blood.
- Hamsters were infected 24 hours later by oral gavage (10 mL/kg) with a suspension of a 48 hour culture of *C. difficile* ATCC 43596, resulting in an inoculum of approximately 1.3×10^7 CFU/hamster.
- At 24 hours post infection, groups of animals (N=10) received an oral dose of omadacycline 50 mg/kg/day, vancomycin 50 mg/kg/day or vehicle (sterile water) for 5 days.
- Animals were observed daily to assess general health; body weight was recorded at least 3 times weekly.
- *In vitro* activity also was determined for clindamycin, tigecycline, vancomycin, and metronidazole.

Data Analysis

- Percent survival for each group was determined for up to 21 days post infection.
- Kaplan-Meier survival analysis was performed with a staircase plot.
- Using a Log Rank analysis of data, p-values, significant difference in curves, and median survival were determined.

RESULTS

- The MIC_{90} for omadacycline against *C. difficile* was 0.06 mg/L by broth dilution and 0.12 mg/L by agar dilution (**Table 1**).
- Omadacycline was more active than doxycycline (MIC_{90} = 0.5 mg/L by broth and 1 mg/L by agar).

Table 1. Minimum Inhibitory Concentration For Omadacycline and Comparators Against *C. difficile* Strains (N=27) by Broth and Agar Dilution Methods

	Minimum Inhibitory Concentration (mg/L)					
	Broth Microdilution			Agar Microdilution		
Drug	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}
Omadacycline	0.06-0.12	0.06	0.06	0.06-0.12	0.12	0.12
Cefotaxime	8->128	64	128	8->128	>64	>128
Doxycycline	0.015-0.5	0.03	0.5	0.03-2	0.03	1
Moxifloxacin	0.12-0.5	0.25	0.5	0.25-1	0.05	1
Metronidazole	0.12-1	0.12	0.5	0.06-0.5	0.12	0.25
Imipenem	0.5-8	4	8	0.5-8	4	8
Clindamycin	0.12->16	4	>16	0.12->16	8	>16

- Against the infection model strain, omadacycline was as active as tigecycline, metronidazole, and vancomycin (MIC_{90} = 0.06 mg/L for all drugs), while clindamycin exhibited no activity (**Table 2**).

Table 2. Minimum Inhibitory Concentration (MIC_{90}) For Omadacycline and Tested Compounds in the Infection Model

	MIC_{90} (mg/L)	
	C. difficile ATCC 43596	
Compound	Plate A	Plate B
Omadacycline	0.06	0.06
Tigecycline	0.06	0.06
Metronidazole	0.06	0.06
Clindamycin	>32	>32
Vancomycin	0.06	0.06

Survival

- Day 2 post infection, 100% of omadacycline treated animals were alive, compared to 40% and 0% for vancomycin and vehicle control animals (**Figure 2**).
- Hamsters receiving only clindamycin pre-treatment demonstrated 100% survival at Day 2 post infection.
- For omadacycline -treated animals, survival declined to 60% by Day 3 and remained at 60% until declining to 40% on Day 13 and to 0% by Day 16.
- Animals treated with vancomycin that survived the initial 2 days began to die by Day 11 (30% survival) and all animals succumbed to infection by Day 14.
- Overall, the median survival for omadacycline-treated animals was 12 days compared to 2 days for vancomycin and 4 days for clindamycin pre-treatment (**Table 3**).

Figure 2. Kaplan-Meier analysis of Percent Survival of Hamsters Infected With *C. difficile* After Treatment With Omadacycline and Comparators.

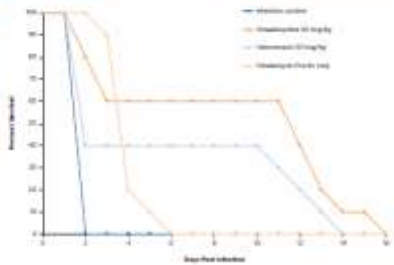


Table 3. Median Survival For Hamsters After Treatment With Omadacycline and Comparators

Test Compound	Median Survival (days)	p-value*
Omadacycline	12	0.0004
Vancomycin	2	0.0188
Clindamycin	4	<0.0001

*Kaplan-Meier analysis using log-rank test

SUMMARY AND CONCLUSIONS

- Omadacycline exhibited potent *in vitro* activity against *C. difficile* that was similar to comparators.
- Omadacycline demonstrated efficacy in the hamster model of *C. difficile*-associated diarrhea that was superior to vancomycin.
- Omadacycline might offer potential for the treatment of *C. difficile* infections.

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PARATEK

Kim

NEUE ANTIBIOTIKA
Lefamulin

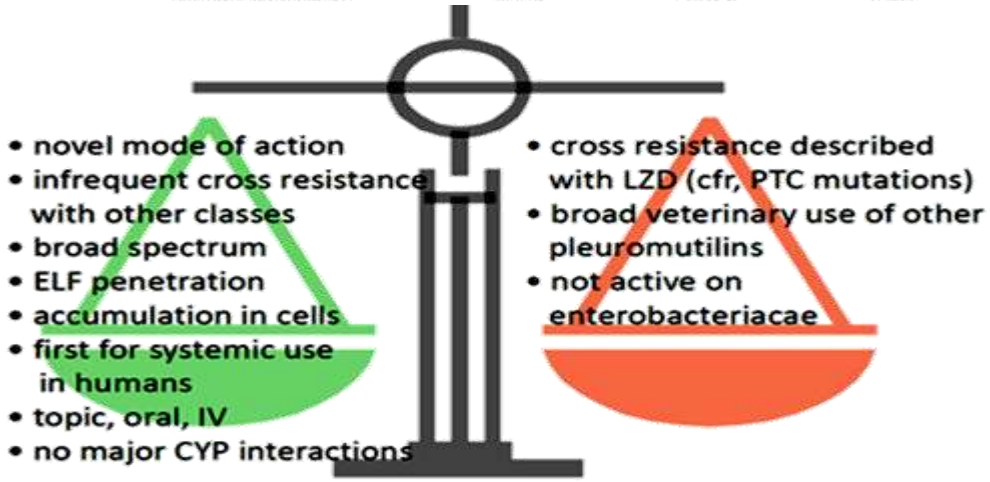
- **Pleuromutiline**
  - selektive Bindung an Ribosomen
- **Retapumilin**
  - 2007 erster humanmed Vertreter (topisch)
- **Herausforderungen**
  - metabolische Stabilität
  - mäßige intrinsische antibakterielle Aktivität
  - begrenzte Räume für chemische Modifikationen

Gram-positive organisms	Lefamulin		Linezolid		Vancomycin		Daptomycin	
	MIC_{50}, µg/ml	MIC_{90}, µg/ml	MIC_{50}, µg/ml	MIC_{90}, µg/ml	MIC_{50}, µg/ml	MIC_{90}, µg/ml	MIC_{50}, µg/ml	MIC_{90}, µg/ml
Staphylococcus aureus (n=5527)	0.12	0.12	1	1	1	1	0.25	0.5
MRSA	0.12	0.25	1	1	1	1	0.25	0.5
β-Hemolytic streptococcus (n=763)	0.03	0.03	1	1	0.25	0.5	≤0.06	0.25
Streptococcus pyogenes, group A Streptococci (n=267)	0.03	0.03	1	1	0.25	0.5	≤0.06	≤0.06
Streptococcus agalactiae, group B Streptococci (n=334)	0.03	0.03	1	1	0.5	0.5	0.12	0.25
Viridans group Streptococcus (n=245)	0.12	0.5	1	1	0.5	0.5	0.25	0.5
Enterococcus faecium (n=536)	0.12	4	1	1	>16	>16	2	2
Streptococcus pneumoniae (n=1473)	0.12	0.25	1	1	0.25	0.5	–	–

Gram-negative organisms	Lefamulin		Azithromycin		Ceftriaxone		Moxifloxacin	
	MIC_{50}, µg/ml	MIC_{90}, µg/ml	MIC_{50}, µg/ml	MIC_{90}, µg/ml	MIC_{50}, µg/ml	MIC_{90}, µg/ml	MIC_{50}, µg/ml	MIC_{90}, µg/ml
Haemophilus influenzae (n=360)	1	2	1	2	≤0.06	≤0.06	≤0.5	≤0.5
Moraxella catarrhalis (n=253)	0.12	0.25	≤0.25	≤0.25	0.25	0.5	≤0.5	≤0.5

Atypical organisms	Lefamulin		Azithromycin		Doxycycline		Moxifloxacin	
	MIC_{50}, µg/ml	MIC_{90}, µg/ml	MIC_{50}, µg/ml	MIC_{90}, µg/ml	MIC_{50}, µg/ml	MIC_{90}, µg/ml	MIC_{50}, µg/ml	MIC_{90}, µg/ml
Legionella pneumophila (n=30)	0.12	0.5	0.06	0.12	–	–	0.06	0.12
Chlamydophila pneumoniae (n=50)	0.02	0.04	–	–	–	–	–	–
Mycoplasma pneumoniae (n=50)	0.006	0.006	–	–	–	–	–	–

MRSA USA300	87.0	94.1	90.5



Kavanagh, Proc Natl Acad Sci 1951 – Schmid, Berl Münch Tierärztl Wochenschr 2014 – Bambeke, ECCMID 2015 – Veve, Pharmacother 2018

NEUE ANTIBIOTIKA
Lefamulin

- **KEINE Kreuzresistenzen zu**
  - Betalaktamantibiotika
  - Chinolonen
  - Glykopeptiden
  - Makroliden
  - Tetracyclinen
- **Fetotoxizität im Tierversuch**
  - Kontrazeption bis zwei Tage nach der letzten Dosis
- **QTc-Intervallverlängerung möglich**

	Patients, n (%)	
	Lefamulin (n = 273)	Moxifloxacin → Linezolid (n = 273)
All TEAEs[a,b]	104 (38.1)	103 (37.7)
Mild	56 (20.5)	62 (22.7)
Moderate	34 (12.5)	28 (10.3)
Severe	14 (5.1)	13 (4.8)
TEAEs occurring in >2% of patients in either group		
Hypokalemia	8 (2.9)	6 (2.2)
Nausea	8 (2.9)	6 (2.2)
Insomnia	8 (2.9)	5 (1.8)
Infusion site pain	8 (2.9)	0
Infusion site phlebitis	6 (2.2)	3 (1.1)
ALT increase	5 (1.8)	6 (2.2)
Hypertension	2 (0.7)	6 (2.2)
Diarrhea	2 (0.7)	21 (7.7)
Treatment-related TEAEs	41 (15.0)	39 (14.3)
Mild	28 (10.3)	30 (11.0)
Moderate	9 (3.3)	6 (2.2)
Severe	4 (1.5)	3 (1.1)
Serious TEAEs	19 (7.0)	13 (4.8)
Treatment-related serious TEAEs[c]	3 (1.1)	1 (0.4)
TEAE leading to death[d]	6 (2.2)	5 (1.8)
TEAE leading to discontinuation of study drug[e]	8 (2.9)	12 (4.4)
TEAE leading to withdrawal from study[f]	5 (1.8)	11 (4.0)

Abbreviations: ALT, alanine aminotransferase; QTcF, QT interval corrected according to Fridericia; TEAE, treatment-emergent adverse event.

[a]A TEAE is defined as an adverse event that starts or worsens with or after the first dose of the study drug.

[b]Per protocol, sites were instructed to report nonserious adverse events through the test-of-cure visit and serious adverse events through late follow-up.

[c]Lefamulin (elevated liver function test, injection site reaction, and ALT increase); moxifloxacin (angioedema).

[d]Lefamulin (ventricular arrhythmia, sepsis, congestive heart failure, myocardial infarction, pneumonia, and chronic obstructive pulmonary disease); moxifloxacin (cerebrovascular accident, testicular seminoma, hematemesis/hemorrhagic shock, cardiac arrest, and death due to natural causes).

[e]Lefamulin (pulmonary tuberculosis, congestive heart failure, pleural empyema, infusion site phlebitis, prolonged QTcF interval, bradycardia, pneumonia, and chronic obstructive pulmonary disease); moxifloxacin (n = 3 prolonged QTcF interval, n = 2 pleural empyema, and n = 1 each for acute respiratory failure/pneumonia, hemorrhagic shock, infusion site erythema, atrial fibrillation/arterial hypertension/pulmonary embolism, confusion, angioedema, and acute cystitis).

[f]Lefamulin (congestive heart failure, myocardial infarction, pneumonia, chronic obstructive pulmonary disease, and pleuritis); moxifloxacin (n = 2 prolonged QTcF interval and n = 1 each for pneumonia, hematemesis/hemorrhagic shock, infusion site erythema, pulmonary embolism, cardiac arrest, death due to natural causes, angioedema, atrial tachycardia/atrial fibrillation/prolonged QTcF interval, and acute cystitis).

File, Clin Infect Dis 2019

NEUE ANTIBIOTIKA
Antibiotika in der Pipeline I

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Expected activity against priority pathogens				Innovation			
				CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Solithromycin	NDA	Macrolide	iv & oral (Melinta/Fujifilm Toyama Chemical)	/	/	/	●	-	-	-	-
Contezolid, Contezolid acefosamil	NDA	Oxazolidinone	oral (MicuRx) iv & oral (MicuRx)	/	/	/	●	-	-	-	-
Sulopenem, Sulopenem etzadroxil/ probenecid	3	Penem	iv (Iterum) oral (Iterum)	○	○	○	/	-	-	-	-
Durlobactam (ETX-2514) + sulbactam	3	DBO-BLI/PBP2 binder + β-lactam-BLI/PBP1,3 binder	iv (Entasis)	●	○	○	/	-	-	-	-
Taniborbactam (VNRX-5133) + cefepime	3	Boronate-BLI + cephalosporin	iv (Venatorx/ GARDP)	○	?	●	/	?	✓	-	-
Enmetazobactam (AAI-101) + cefepime	3	β-lactam BLI + cephalosporin	iv (Allecra)	○	○	○	/	-	-	-	-
Zoliflodacin	3	Topoisomerase inhibitor (spiropyrimidenetrione)	oral (Entasis/GARDP)	/	/	/	●	✓	✓	-	✓
Gepotidacin	3	Topoisomerase inhibitor (triazaacenaphthylene)	iv & oral (GSK)	/	/	/	●	?	✓	-	✓

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NEUE ANTIBIOTIKA
Antibiotika in der Pipeline II

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Expected activity against priority pathogens				Innovation			
				CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Afabicin (Debio-1450)	2	FabI inhibitor	iv & oral (Debiopharm)	/	/	/	●	✓	✓	✓	✓
Nafithromycin (WCK-4873)	2	Macrolide	oral (Wockhardt)	/	/	/	●	-	-	-	-
TNP-2092	2	Rifamycin-quinolizinone hybrid	iv & oral (TenNor)	/	/	/	?	-	-	-	-
Benapenem	2	Carbapenem	iv (Sichuan Pharmaceutical)	○	○	○	/	-	-	-	-
Zidebactam + cefepime	1	DBO-BLI/PBP2 binder + cephalosporin	iv (Wockhardt)	●	●	●	/	-	-	-	-
Nacubactam + meropenem	1	DBO-BLI/PBP2 binder + meropenem	iv (NacuGen Therapeutics)	○	○	●	/	-	-	-	-
ETX0282 + cefpodoxime	1	DBO-BLI/PBP2 binder + cephalosporin	oral (Entasis)	○	○	●	/	-	-	-	-
VNRX-7145 + ceftibuten	1	Boronate-BLI + cephalosporin	oral (Venatorx)	○	○	●	/	?	✓	-	-

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NEUE ANTIBIOTIKA
Antibiotika in der Pipeline III

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Expected activity against priority pathogens				Innovation			
				CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
SPR-206	1	Polymyxin	iv (Spero)	●	●	●	/	-	-	-	-
KBP-7072	1	Tetracycline	oral (KBP BioSciences)	●	○	○	●	-	-	-	-
TP-271	1	Tetracycline	iv & oral (La Jolla Pharmaceutical)	?	○	○	●	-	-	-	-
TP-6076	1	Tetracycline	iv (La Jolla Pharmaceutical)	●	○	?	/	-	-	-	-
EBL-10031 (apramycin)	1	Aminoglycoside	iv (Juvabis)	?	○	?	/	-	-	-	-
TNP-2198	1	Rifamycin-nitroimidazole conjugate	oral (TenNor)	/	/	/	●	-	-	-	-
TXA-709	1	FtsZ inhibitor	oral & iv (Taxis)	○	○	○	●	✓	✓	✓	✓
ARX-1796 (oral avibactam prodrug)	1	DBO-BLI + β-lactam	oral (Arixa Pharmaceuticals)	○	○	●	/	-	-	-	-
PLG0206 (WLBU2)	1	Cationic peptide	iv (Peptilogics)	?	?	?	●	?	✓	?	?
QPX7728 + QPX2014	1	Boronate-BLI + unknown	iv (Qpex Biopharma)	●	?	●	/	?	-	-	-

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NEUE ANTIBIOTIKA
Betalaktame/Betalaktamasehemmer

	CRE				CRAB	CRPA
	A	A	D	B		
	ESBL (CTX-M)	KPC (KPC-2,-3)	OXA (OXA-48)	MBL (NDM)		
Vaborbactam + meropenem	●	●	●	-	-	-
Relebactam + imipenem/cilastatin	●	●	●	-	-	?
Cefiderocol	●	●	●	●	●	●
Sulopenem	●	-	-	-	-	-
Durlobactam (ETX-2514) + sulbactam	-	-	-	-	●	-
Taniborbactam (VNRX-5133) + cefepime	●	●	●	●	-	?
Enmetazobactam (AAI-101) + cefepime	●	?	-	-	-	-
Zidebactam + cefepime	●	●	●	?	-	?
Nacubactam + meropenem	●	●	●	?	-	-
ETX-0282 + cefpodoxime	●	●	●	-	-	-
VNRX-7145 + ceftibuten	●	●	●	-	-	-
ARX-1796 (oral avibactam prodrug)	●	●	●	-	-	-
QPX7728 + QPX2014	●	●	●	●	?	-

Pathogen activity: ● active; ? possibly active, - not or insufficiently active or activity not assessed.

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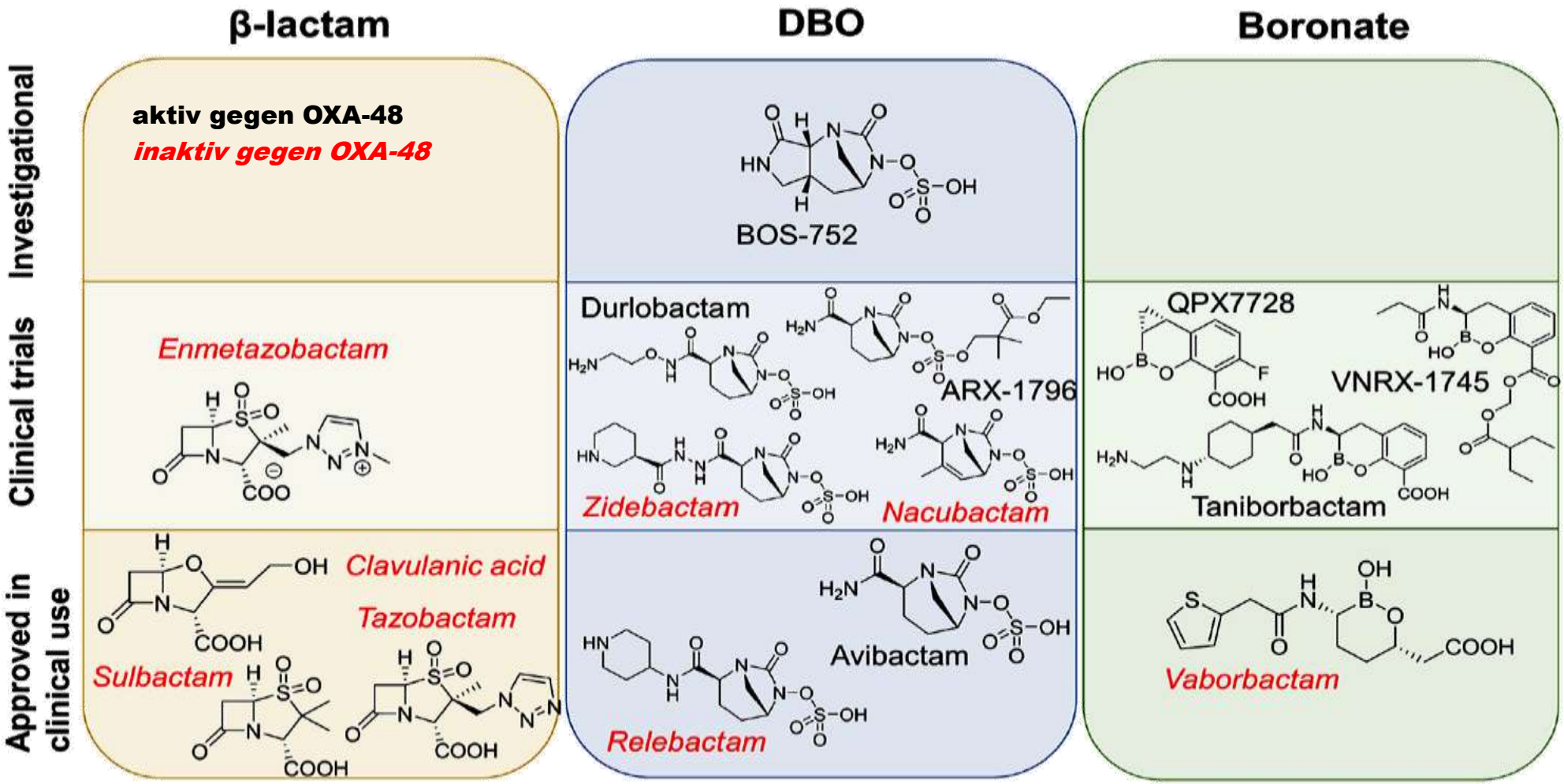
NEUE ANTIBIOTIKA
Betalaktamasehemmer



Hirvonen, Antimicrob Agents Chemother 2021

NEUE ANTIBIOTIKA
Betalaktamasen & ihre Hemmer

Molecular Class	Enzymes	Activity against Penicillins	Activity against Cephalosporins	Activity against Carbapenems	Activity against Aztreonam	Inhibited by Carbapenems	Inhibited by Clavulanic Acid	Inhibited by Tazobactam	Inhibited by Avibactam	Inhibited by Vaborbactam and Relebactam	Relevant Organisms	Geographic Distribution
A (serine penicillinases)	ESBL (TEM, SHV, CTX-M, others)	Yes	Yes, except cefamycins	No	Yes	Yes	Yes	Yes	Yes	Yes	*E. coli* *Klebsiella* spp. *P. mirabilis*	Worldwide spread. Community and nosocomial infections
	KPC	Yes	Yes	Yes Strong activity	Yes	No	No	No	Yes	Yes	*E. coli* *K. pneumoniae* *K. oxytoca* *S. marcescens* *Enterobacter* spp. *C. freundii*	Worldwide United States South and Central America Europe (mainly Italy and Greece)
B (metallo-β-lactamases)	MBLs (VIM, IMP, NDM, others)	Yes	Yes	Yes Strong activity	No	No	No	No	No	Yes	*E. coli* *K. pneumoniae* *K. oxytoca,* *S. marcescens,* *Enterobacter* spp. *C. freundii*	NDM: Asia (mainly India, Pakistan and Bangladesh); Italy (Tuscany) IMP and VIM: Europe (Romania, Poland and Denmark)
C (cephalosporinases)	AmpC type (CMY-2, DHA-1, FOX-1, others)	Yes	Yes except cefepime, including cefamycins	No	Yes	Yes	No	No High concentrations	Yes	Yes	*K. pneumoniae* *E. coli* *Enterobacter* spp. *S. enteritidis* *C. freundii* *S. marcescens* *A.baumannii*	Worldwide spread. Community and nosocomial infections
D (oxacillinases)	OXA (OXA-48, OXA-23, OXA-11, OXA-181, others)	Yes §	Yes Weak activity against cefepime and ceftazidime	Yes Weak activity *	Yes	No	Weak	Weak	Yes	No	*A. baumannii* *P. aeruginosa* *E.coli* *K. pneumoniae* *P. mirabilis* *C. freundii*	Relatively common in Europe (Mediterranean countries), Northern Africa and Middle Eastern countries Extremely rare in United States

Abbreviation: ESBL, Extended-spectrum β-lactamases; IMP, Imipenemase Metallo-beta-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; MBLs, metallo-β-lactamases; NDM, New Delhi metallo-betalactamase; OXA-48, oxacillinase-48; OXA-23, oxacillinase-23; VIM, Verona integron-encoded metallo-beta-lactamase. § Except cloxacillin * High-level carbapenem resistance may occur when these enzymes are found in combination with other β-lactamases (ESBL-od Amp-C), or with membrane permeability alteration.

Bassetti, Antibiotics 2020

NEUE ANTIBIOTIKA
MRGN-Aktivität im Vergleich

	ESBL	CRE-KPC	CRE-OXA48	CRE-MBL	DTR *P. Aeruginosa*	DTR *Acinetobacter*
BL/BLI Combination						
• Ceftolozane/Tazobactam	🟢	🔴	🔴	🔴	1 🟢	🔴
• Ceftazidime-Avibactam	🟢	🟢	🟢	🔴	🟢	🔴
• Imipenem-Relebactam	🟢	🟢	2 🔴	🔴	3 🟢	🔴
• Meropenem-Vaborbactam	🟢	🟢	🔴	🔴	🔴	🔴
• Aztreonam-Avibactam	🟢	🟢	🟢	4 🟢	5 🔴	🔴
• Cefepime/Zidebactam	🟢	🟢	🟢	🟢	🟢	🟢
• Meropenem/Nacubactam	🟢	🟢	🟢	🔴	🔴	🔴
• Ceftaroline/Avibactam	🟢	🟢	🟢	🔴	🔴	🔴
Novel Cephalosporine						
• Cefiderocol	🟢	🟢	🟢	🟢	🟢	🟢
Novel Amynoglicoside						
• Plazomicin	🟢	🟢	6 🟢	7 🟢	8 🔴	8 🔴
Novel Tetracycline						
• Eravacyclin	🟢	🟢	🟢	🟢	🔴	🟢
• Murepavadin	🔴	🔴	🔴	🔴	🟢	🔴

1. Decreased activity for carbapenemase- producing strains of CR *P. aeruginosa*;
2. Very weak activity; 3. Not have activity against MBL; 4. Reduced activity against certain NDM *Escherichia coli* isolates; 5. Activity comparable to aztreonam alone; 6. Activity against OXA-type CREs but increased resistance is observed; 7. Not active against many NDMs; 8. Activity toward *P. aeruginosa* and *A. baumannii* is overall comparable to existing aminoglycosides (tobramycin, amikacin, gentamicin).

Bassetti, Antibiotics 2020

NEUE ANTIBIOTIKA
Aus alt mach neu

CEFEPIM

	BLI class	ESBL	KPC	OXA-48	MBL	MDR *P. aeruginosa*
Cefepime/zidebactam	DBO	✓	✓	✓	✓	✓
Cefepime/taniborbactam	Boronic acid	✓	✓	✓	✓/—[a]	✓/—
Cefepime/enmetazobactam	Penicillanic acid sulfone	✓	—	—	—	—
Cefepime/tazobactam	Penicillanic acid sulfone	✓	—	—	—	—

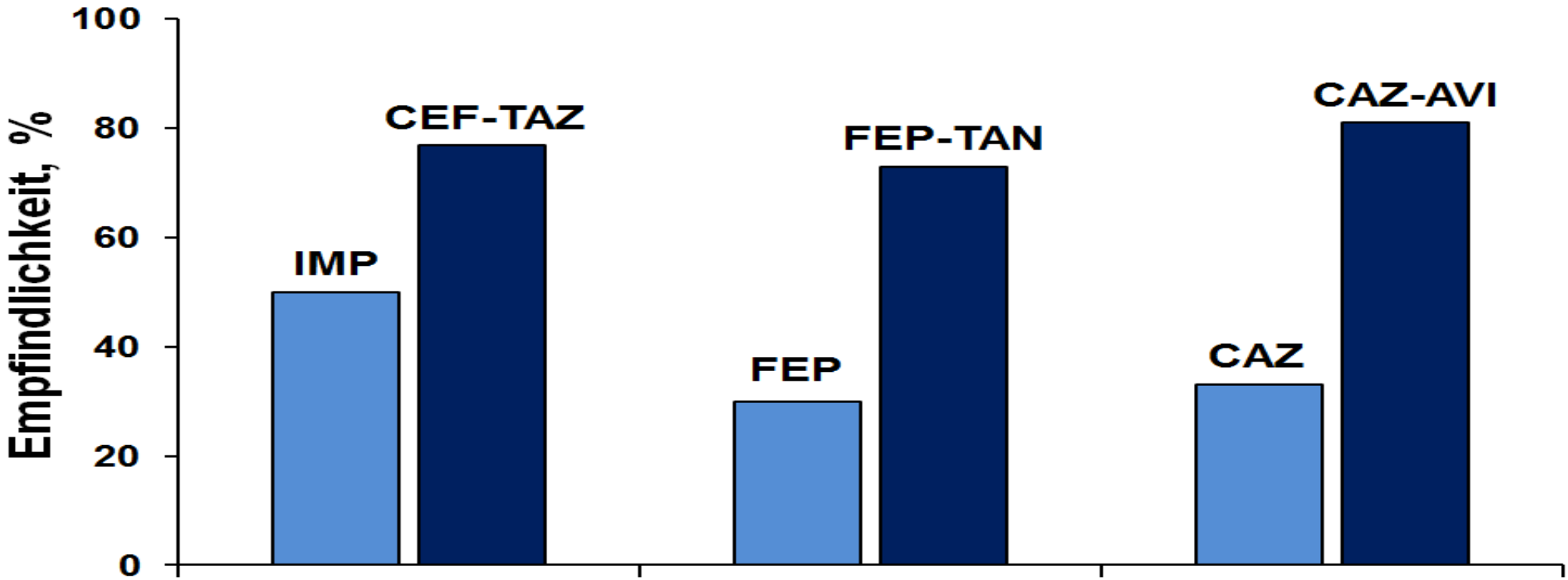
[a]Not inhibitory against IMP-type MBLs.

& Co

Isler, J Antimicrob Chemother 2021

NEUE ANTIBIOTIKA
Cefepim/Tazobactam & Taniborbactam

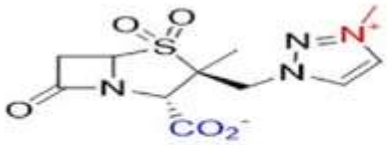
- **100 klinische Pseudomonas-Isolate**
- **74% MDR/XDR**

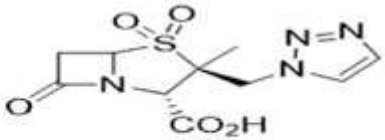


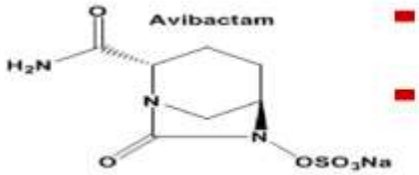
Shields, A5956, ECCMID 2020 – Gill, J Antimicrob Chemother 2021

NEUE ANTIBIOTIKA
Cefepim/Enmetazobactam

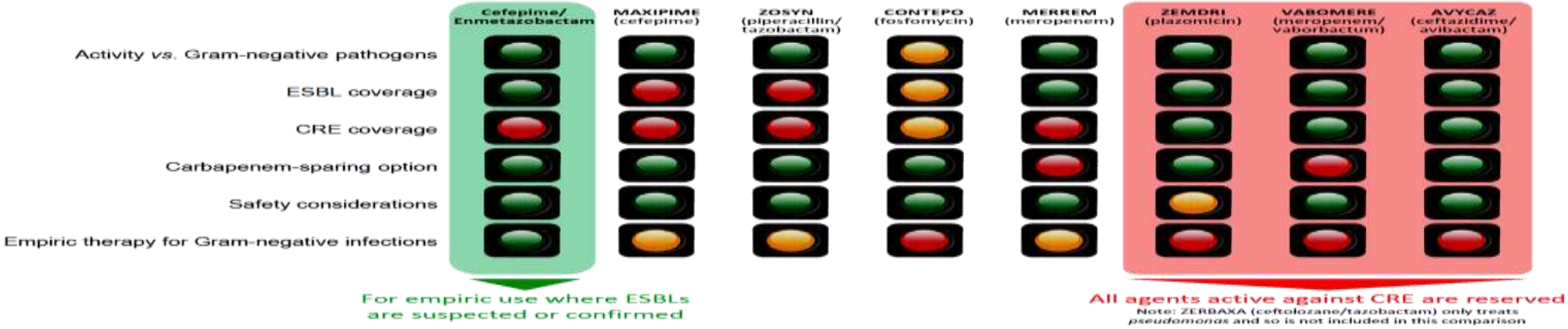
Agent	MIC$_{90}$s and % susceptible Gram-negatives, 2016-18 US / EU									
	Enterobacterales								*P. aeruginosa*	
	All		3GC-resistant		ESBL co-producing		ESBL-only producing			
	n = 7168		n = 1416 (20%)		n = 801 (11%)		n = 722 (10%)		n = 846	
	MIC$_{90}$	%S	MIC$_{90}$	%S	MIC$_{90}$	%S	MIC$_{90}$	%S	MIC$_{90}$	%S
Cefepime-enmetazobactam*	0.25	98 – 99	2	92 – 94	0.5	99 – 100	0.25	99 – 100	16	85.9
Cefepime	16	87	>64	36	>64	12	>64	12	16	79
Piperacillin-tazobactam	32	87	>256	51	256	71	128	75	128	76
Meropenem	0.06	98	4	88	0.12	96	0.06	99	16	77
Ceftolozane-tazobactam (Zerbaxa)	1	93	64	64	16	82	4	87	2	96
Ceftazidime-avibactam (Avycaz)	0.25	100	1	98	0.5	100	0.5	100	8	95







- **Cefepim**
  - stabil gegen AmpC, OXA-48
- **Enmetazobactam**
  - hemmt ESBL



Papp-Wallace, Antimicrob Agents Chemother 2019 – Allecra Therapeutics Data on file

NEUE ANTIBIOTIKA
Clavulansäure & Oralcephalosporine

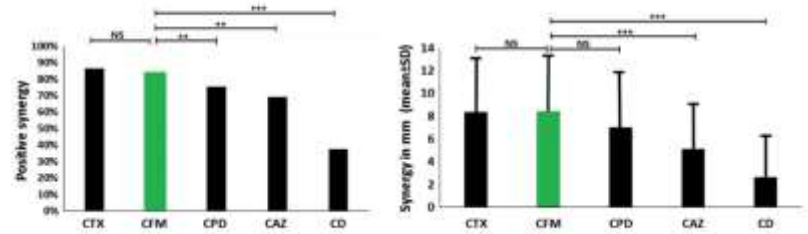
- **Cefixime plus Amoxi/Clav**
  - Aktivität gegen ESBL (CTX-M-15)
    - E. coli, Klebsiella spp.
  - KEINE Aktivität gegen AmpC
  - immer mikrobiolog Testung
- **Cefalexin plus Amoxi/Clav**
  - CDI-Risiko geringer, da Cefalexin nicht fäkal ausgeschieden
- **Amoxi/Clav plus**
  - Cefdinir, Cefpodoxim
  - Ceftibuten

Ceftibuten plus Amoxi/Clav

Organism	ESBL Enzyme	Amoxicillin-Clavulanate MIC (µg/mL)	Ciprofloxacin MIC (µg/mL)	C-Scape MIC (µg/mL)
E. coli	CTX-M-15,TEM-1	16	≤0.03	0.5
E. coli	CTX-M-15,TEM-1	8	>4	0.5
E. coli	CTX-M-14	8	≤0.03	0.5
K. pneumoniae	SHV-5,TEM-1	8	0.25	0.12
K. pneumoniae	SHV WT,CTX-M-15, OXA-1/30-like	16	1	0.5
K. pneumoniae	SHV-11,SHV-12,TEM-1	8	>4	0.25
K. pneumoniae	SHV-30	8	0.12	0.25
P. mirabilis	CTX-M-15-like,TEM WT	2	≤0.03	0.03
P. mirabilis	CTX-M-14-like,TEM WT	8	4	0.03
P. mirabilis	None	0.5	>4	<0.015
P. mirabilis	None	1	≤0.03	<0.015
E. coli	None	8	>4	0.25
K. pneumoniae	None	2	>4	0.06

Cefexim plus Clavulansäure

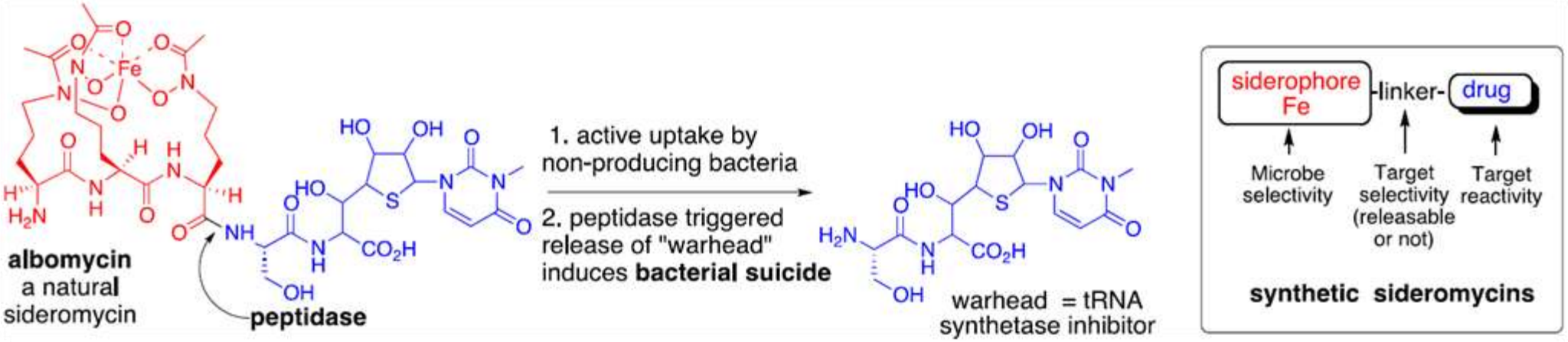
Cefixim 8 mg/kg KG 1x tgl ~ 2 x 0.4 (0.8) g p.o.
Amoxi/Clav 15 – 25 mg/kg KG 2x tgl ~ 2 x 1.5 g p.o.

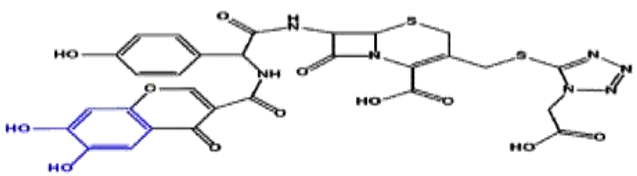


CTX ... Cefotaxim, CFM ... Cefixim, CPD ... Cefpodoxim, CAZ ... Ceftazidim, CD ... Cefdinir

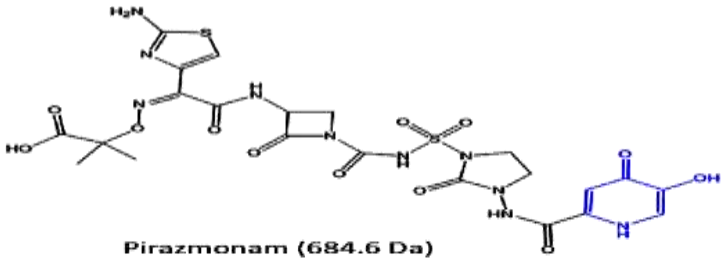
Livermore, Int J Antimicrob Chemother 2011 – Bingen, Antimicrob Agents Chemother 2013 – Jubb, Achaogen 2017
Hawkey, J Antimicrob Chemother 2018 – Al-Tamimi, Microbiol Drug Res 2019

NEUE ANTIBIOTIKA
Synthetische Siderophore

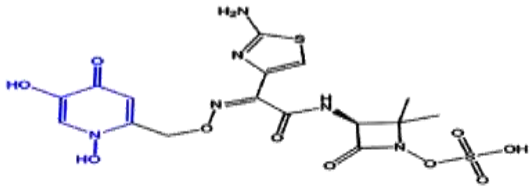




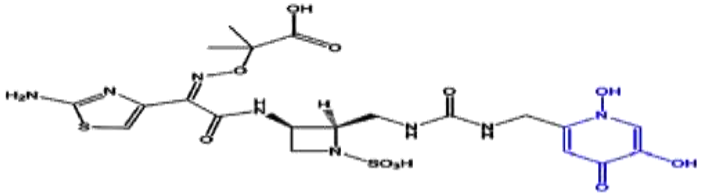
E0702 (725.7 Da)



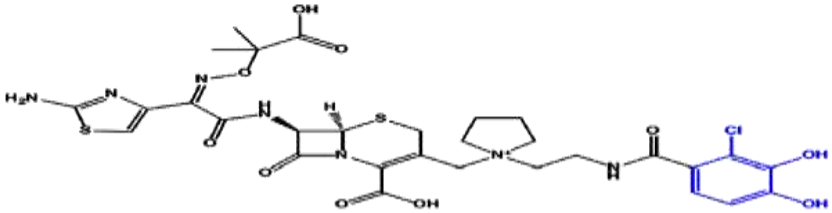
Pirazmonam (684.6 Da)



BAL30072 (518.5 Da)



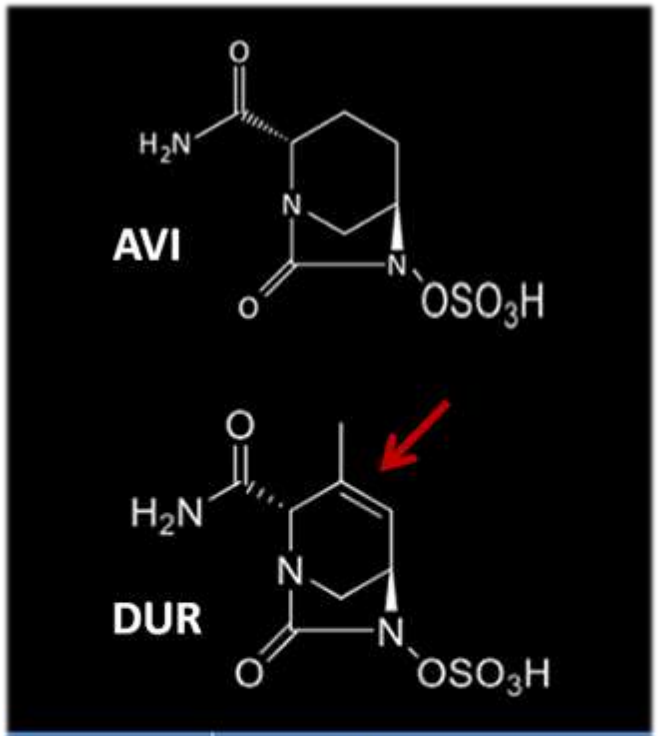
MB-1 (618.6 Da)



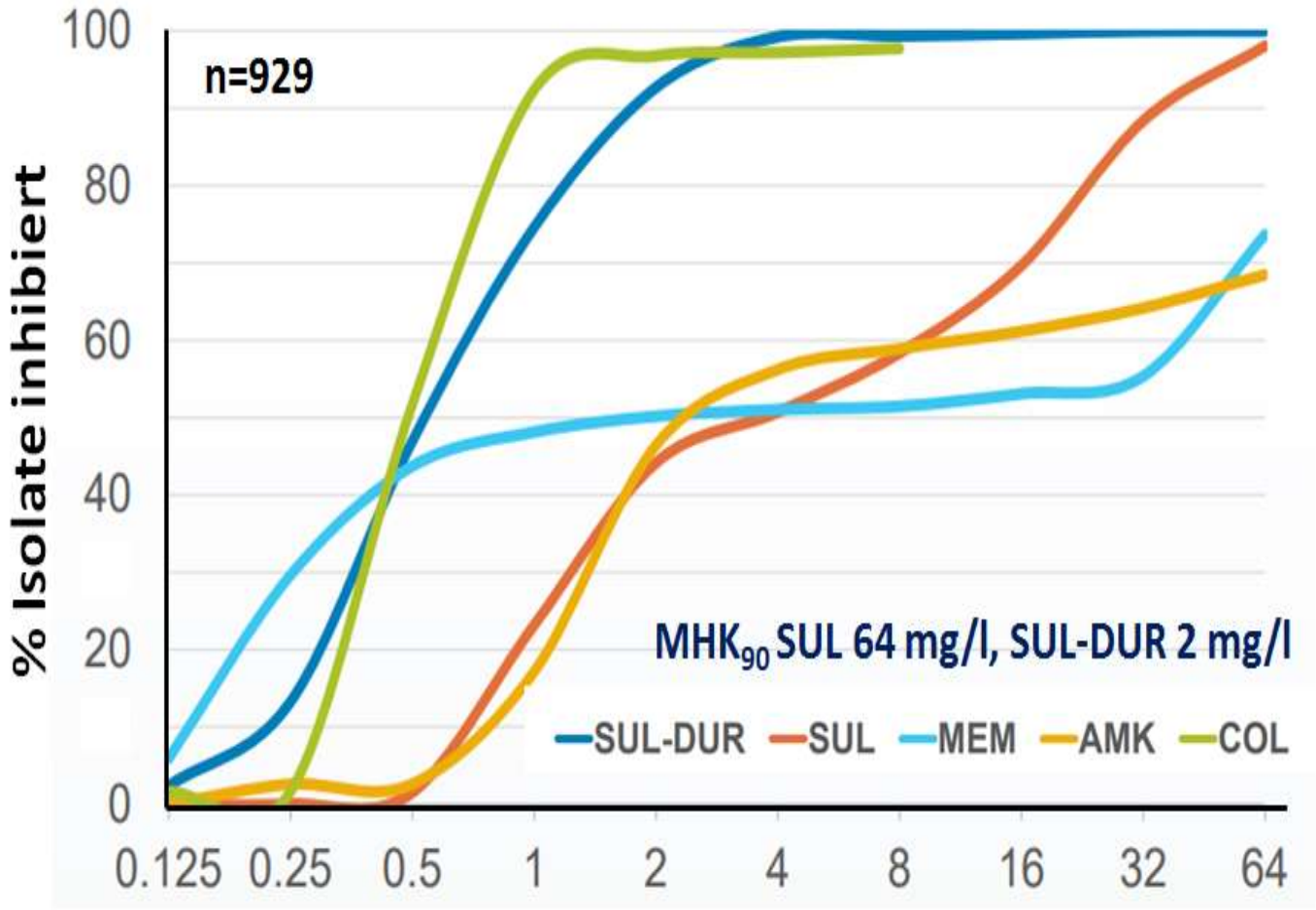
Cefidericol (FETROJA, FDC; 753.2 Da)

Miller, Acc Chem Res 2021 – Klebba, Chem Rev 2021

NEUE ANTIBIOTIKA
Sulbactam/Durlobactam

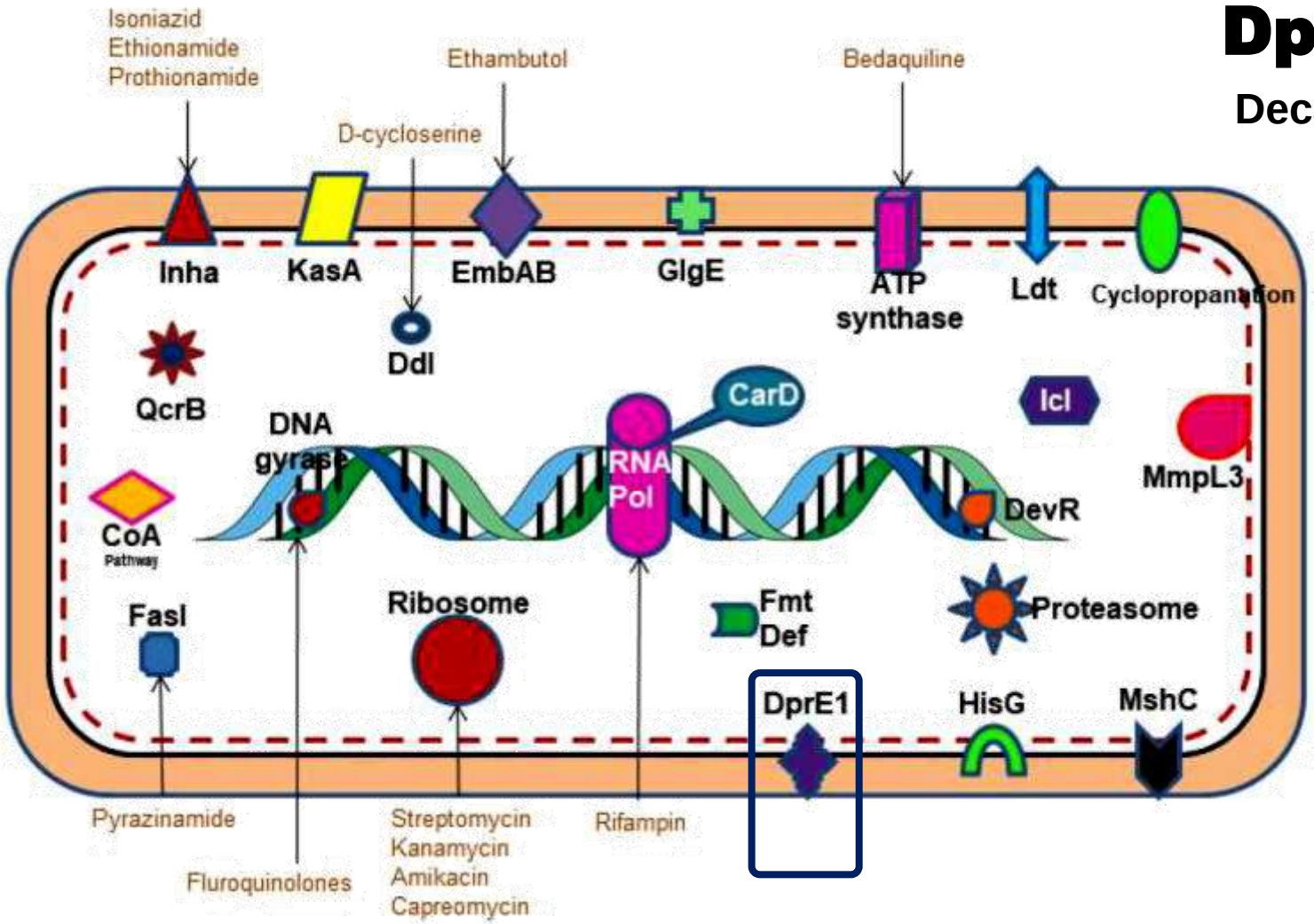


	MHK_{90}, mg/l	
	SUL	SUL-DUR
n=246	64	2



Seifert, J Antimicrob Chemother 2020 – McLeod, P1254, ID Week 2020

NEUE ANTIBIOTIKA
Tuberkulostatika



DprE1-Hemmer

Decaprenyl-phosphoryl-β-D-ribose 2′-epimerase

essentiell für Zellwand-synthese

Chikhale, J Med Chem 2021

NEUE ANTIBIOTIKA
mAk & Co

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Expected activity against priority pathogens
AR-301 (tosatoxumab)	3	Anti-*S. aureus* immunoglobulin M (IgM) monoclonal antibody	iv (Aridis)	*S. aureus*
CF-301 (exebacase)	3	Phage endolysin	iv (ContraFect)	*S. aureus*
SER-109	3	Live biotherapeutic product	oral (Seres Therapeutics)	*C. difficile*
AB103 (reltecimod)	3	Antagonist of both superantigen exotoxins and the CD28 T-cell	iv (Atox Bio)	*S. aureus*
SYN-004 (ribaxamase)	2b	Antibiotic inactivator	oral (Synthetic Biologics)	*C. difficile*
OligoG (CF-5/20)	2b	Alginate oligosaccharide (G-block) fragment	Inhalation (AlgiPharma AS)	*P. aeruginosa*
SAL-200 (tonabacase)	2a	Phage endolysin	iv (iNtRON Biotechnology, Roivant Sciences)	*S. aureus*
AR-101 (panobacumab, Aerumab)	2a	Anti-*P. aeruginosa* serotype O11 IgG monoclonal antibody	iv (Aridis, Shenzen Arimab Biopharma)	*P. aeruginosa*
BT588 (trimodulin)	2	Human plasma-derived native polyvalent antibody preparation containing IgM, IgA and IgG	iv (Biotest)	*S. aureus*
MEDI-4893 (suvratoxumab)	2	Anti-*S. aureus* IgG monoclonal antibody	iv (AstraZeneca)	*S. aureus*

WHO 2020

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www.infektiologie.wien