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UK RUB UNIVERSITÄTSKLINIKUM DER
RUHR-UNIVERSITÄT BOCHUM
RUB
Multiresistente gram-negative Erreger:
Neue Therapien, neue Probleme.

Interessenskonflikte

u.a. Vortragshonorare, Beratertätigkeit, Reise- und Kongressunterstützung, Forschungsunterstützung

- Astute Medical GmbH / bioMérieux Deutschland
- Alexion Pharma Germany
- Bayer Vital GmbH
- Biotest AG
- CSL Behring GmbH
- Eumedica S.A.
- Grünenthal GmbH
- Mitsubishi Tanabe Pharma GmbH
- MSD Sharp & Dohme GmbH
- Pfizer Deutschland GmbH
- Portola Pharmaceuticals
- Shionogi GmbH

Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis

*Alessandro Cassini, Liselotte Diaz Högberg, Diamantis Plachouras, Annalisa Quattrocchi, Ana Hoxha, Gunnar Skov Simonsen, Mélanie Colomb-Cotinat, Mirjam E Kretzschmar, Brecht Devleesschauwer, Michele Cecchini, Driss Ait Ouakrim, Tiago Cravo Oliveira, Marc J Struelens, Carl Suetens, Dominique L Monnet, and the Burden of AMR Collaborative Group**

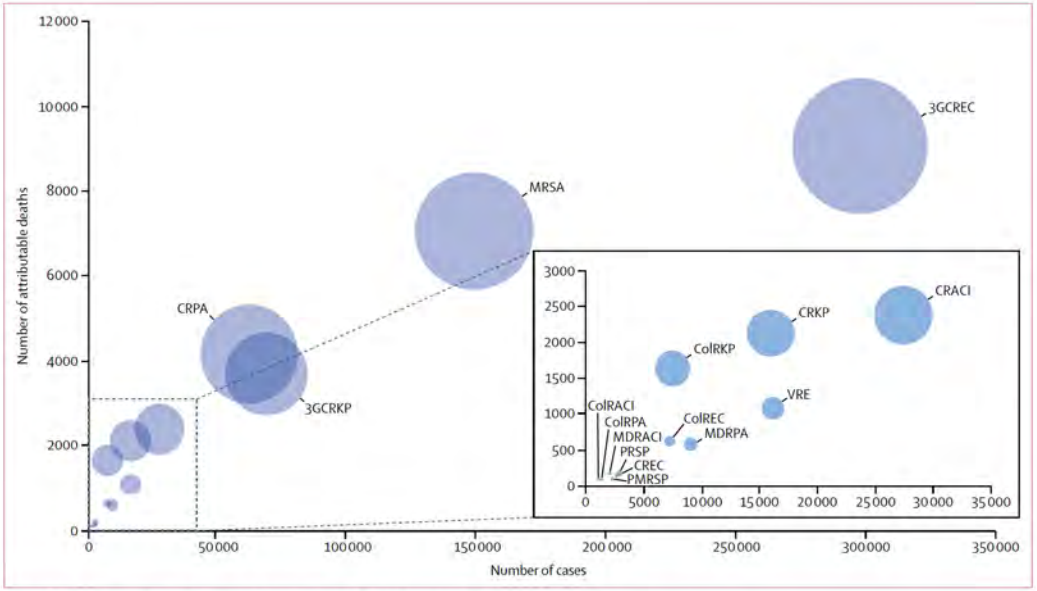

Figure 1: **Infections with antibiotic-resistant bacteria, EU and European Economic Area, 2015**
Diameter of bubbles represents the number of disability-adjusted life-years. ColRACI=colistin-resistant *Acinetobacter* spp. CRACI=carbapenem-resistant *Acinetobacter* spp. MDRACI=multidrug-resistant *Acinetobacter* spp. VRE=vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium*. ColREC=colistin-resistant *Escherichia coli*. CREC=carbapenem-resistant *E coli*. 3GCREC=third-generation cephalosporin-resistant *E coli*. ColRKP=colistin-resistant *Klebsiella pneumoniae*. CRKP=carbapenem-resistant *K pneumoniae*. 3GCRKP=third-generation cephalosporin-resistant *K pneumoniae*. ColRPA=colistin-resistant *Pseudomonas aeruginosa*. CRPA=carbapenem-resistant *P aeruginosa*. MDRPA=multidrug-resistant *P aeruginosa*. MRSA=meticillin-resistant *Staphylococcus aureus*. PRSP=penicillin-resistant *Streptococcus pneumoniae*. PMRSP=penicillin-resistant and macrolide-resistant *S pneumoniae*.

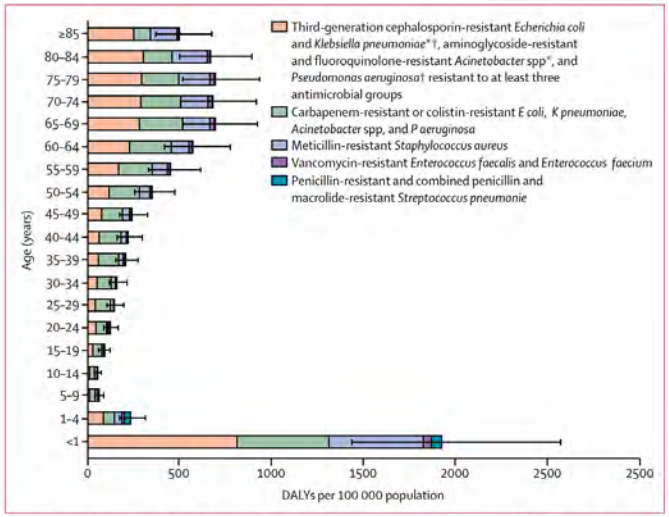

Figure 2: **Model estimates of the burden of infections with antibiotic-resistant bacteria of public health importance in DALYs, by age group, EU and European Economic Area, 2015**
Error bars are 95% uncertainty intervals. DALYs=disability-adjusted life-years. *Excludes those resistant to carbapenem or colistin. †In 2015, most of the third-generation cephalosporin-resistant *E coli* (88·6%) and *K pneumoniae* (85·3%) isolates reported to the European Antimicrobial Resistance Surveillance Network produced an extended-spectrum β-lactamase.[9]

Cassini A, et al. Lancet Infect Dis. 2019;19(1):56-66.

Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis

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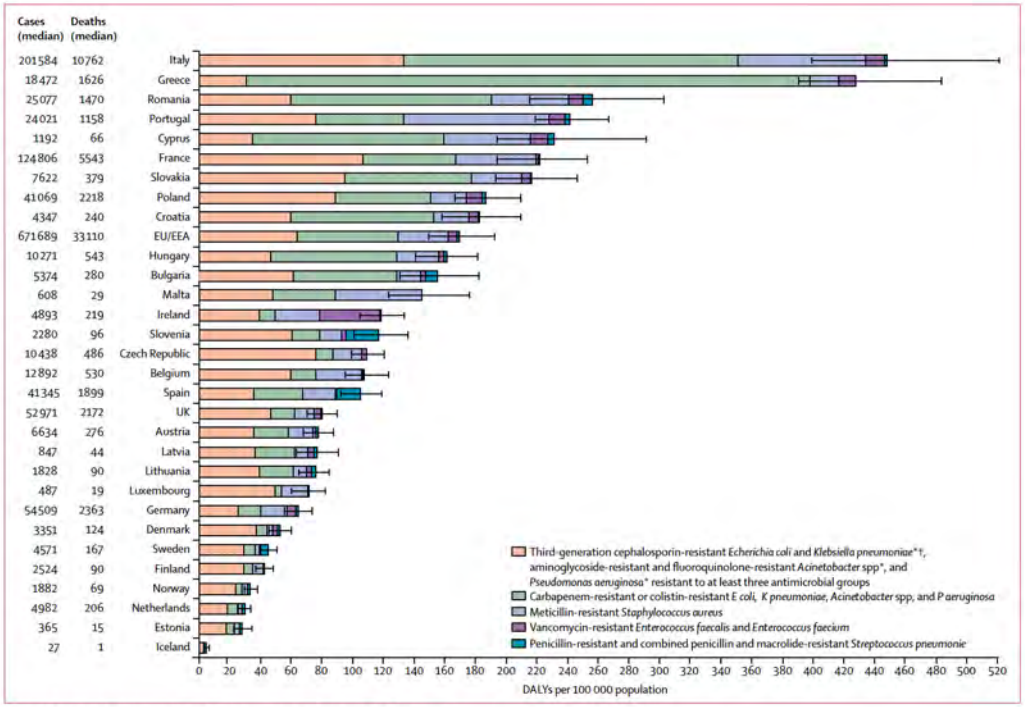


Figure 3: **Burden of infections with antibiotic-resistant bacteria in DALYs, EU and European Economic Area, 2015**
Error bars are 95% uncertainty intervals. Greece did not report data on *S pneumoniae* isolates to the European Antimicrobial Resistance Surveillance Network in 2015. DALY rates are age-standardised to limit the effect of demographic differences across countries; numbers of cases and deaths are not age-standardised. DALYs=disability-adjusted life-years. *Excludes those resistant to carbapenem or colistin. †In 2015, most of the third-generation cephalosporin-resistant *E coli* (88·6%) and *K pneumoniae* (85·3%) isolates reported to the European Antimicrobial Resistance Surveillance Network produced an extended-spectrum β-lactamase.[5]

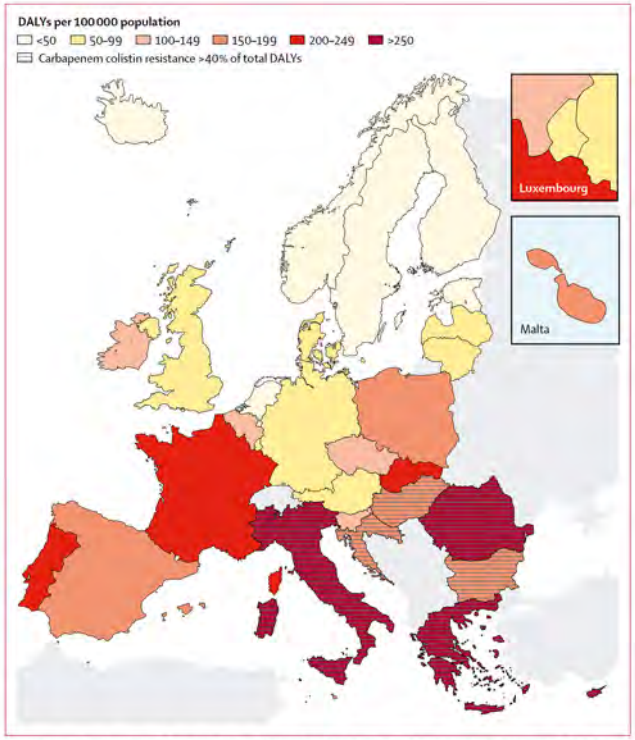


Figure 4: **Model estimates of the burden of infections with selected antibiotic-resistant bacteria of public health importance in DALYs per 100 000 population, EU and European Economic Area, 2015**
Greece did not report data on *S pneumoniae* isolates to the European Antimicrobial Resistance Surveillance Network in 2015. DALYs=disability-adjusted life-years.

Cassini A, et al. Lancet Infect Dis. 2019;19(1):56-66.

ESKAPE

Enterobacterales
(ESBL- und Carbapenemase-Bildner) (*gramnegativ*)

Staphylococcus aureus
(Methicillin-resistent, MRSA) (*grampositiv*)

Klebsiella pneumoniae
(Carbapenemase/KPC-Produzenten) (*gramnegativ*)

Acinetobacter baumannii
(Multi-drug-resistant, MDR) (*gramnegativ*)

Pseudomonas aeruginosa
(Multi-drug-resistant, MDR) (*gramnegativ*)

Enterokokken
(Vancomycin-resistent, VRE) (*grampositiv*)

Boucher WW et al. Clin Inf Dis 2009;48(1):1-12.

RKI-Definition
MRGN

Antibiotikagruppe	Leitsubstanz	Enterobacterales		*Pseudomonas aeruginosa*		*Acinetobacter baumannii*	
		3MRGN[1]	4MRGN[2]	3MRGN[1]	4MRGN[2]	3MRGN[1]	4MRGN[2]
Acylureidopenicilline	Piperacillin	R	R	Nur eine der 4 Antibiotikagruppen wirksam (S oder I)	R	R	R
3./4. Generations-Cephalosporine	Cefotaxim und/ oder Ceftazidim	R	R		R	R	R
Carbapeneme	Imipenem und/ oder Meropenem	S oder I	R		R	S oder I	R
Fluorchinolone	Ciprofloxacin	R	R		R	R	R
			oder Nachweis einer Carbapenemase[3]		oder Nachweis einer Carbapenemase[3]		oder Nachweis einer Carbapenemase[3]

Tab. 2: Neue Klassifizierung multiresistenter gramnegativer Stäbchen auf Basis ihrer phänotypischen Resistenzeigenschaften bei Anwendung des EUCAST-Systems

(R = resistent, I = sensibel bei erhöhter *(Increased)* Dosierung/Exposition, S = sensibel bei normaler Dosierung)

1 3MRGN (**M**ultiresistente **g**ram**n**egative Stäbchen mit Resistenz gegen **3** der 4 Antibiotikagruppen)

2 4MRGN (**M**ultiresistente **g**ram**n**egative Stäbchen mit Resistenz gegen **4** der 4 Antibiotikagruppen)

3 Unabhängig vom Ergebnis der phänotypischen Resistenzbestimmung für Carbapeneme sowie der anderen drei Substanzklassen

RKI, Epidemiologisches Bulletin 2019; Nr. 9.

Resistenzmechanismen
bei grampositiven und gramnegativen Erregern

grampositive Bakterien

Wenige & funktionell ähnliche Resistenz-mechanismen

VAN-A

VAN-B

VAN - C *bis* *VAN-N*

mecA

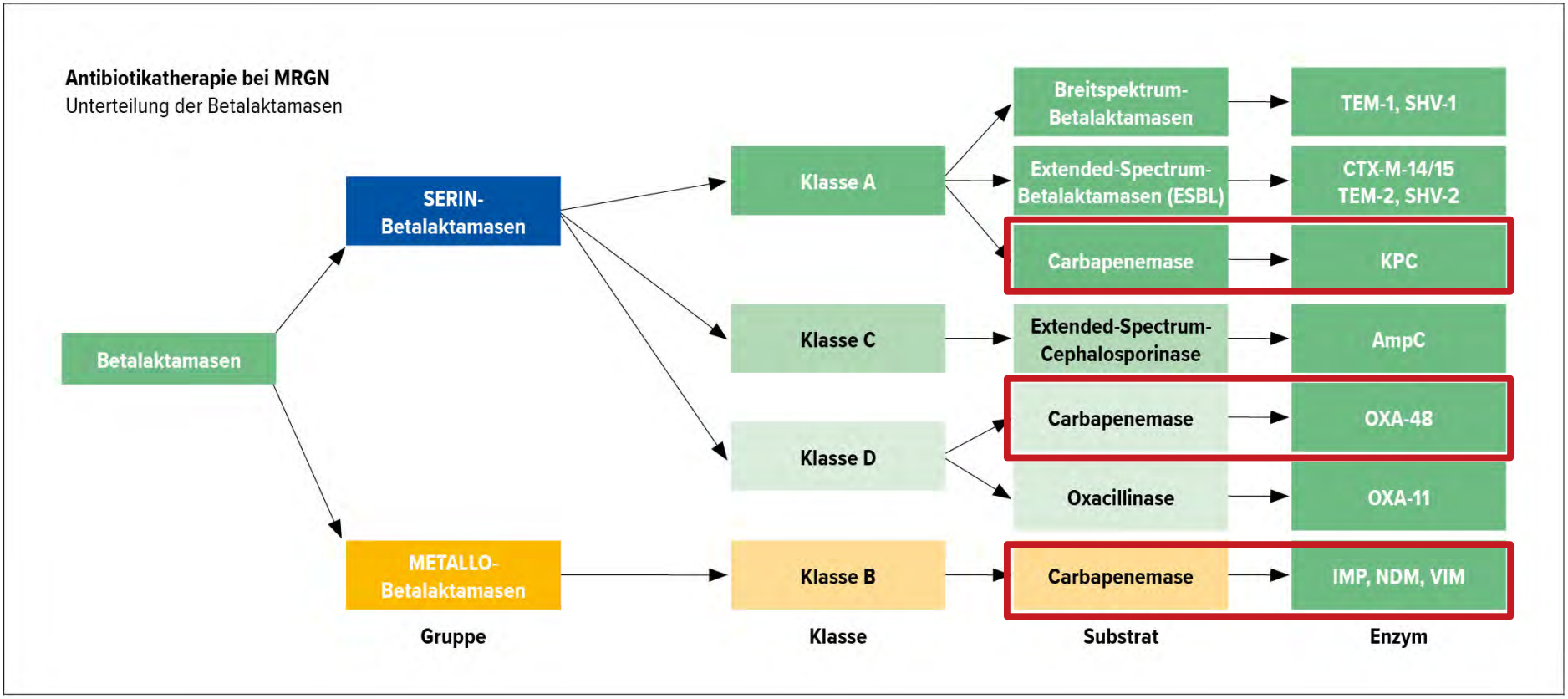
mecC

vs.

gramnegative Bakterien

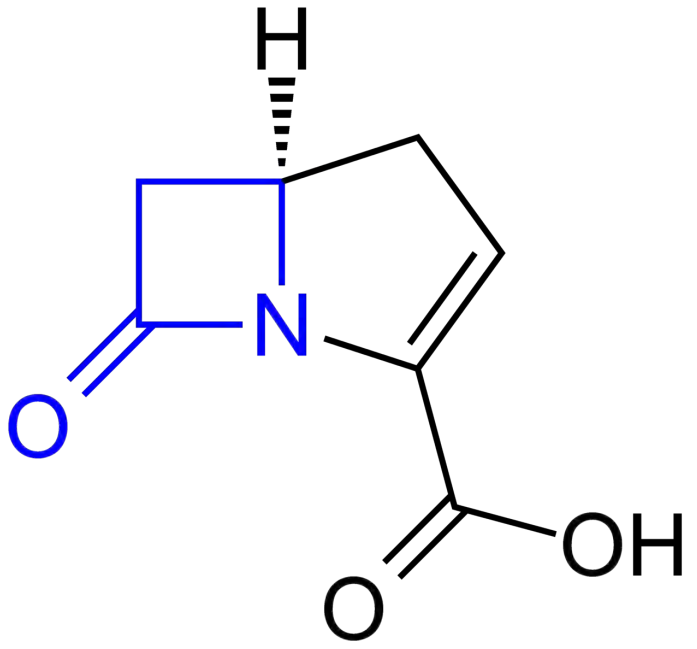
OXA-204 IMP-14 CTX-M-1 **OXA-23**
KPC-2 CTX-M-9 GES-2 IMP-8
SPM-1
GIM-1 GES-1 TEM-58
CTX-M-14 AIM-1
FIM-1 SHV-2
>200 Resistenz-mechanismen VEB-1
OXA-72 **VIM-2** **KPC-3** PER-1
NDM-1 SME-1 SIM-1 OXA-58
IMI-1 **OXA-48** **VIM-1**
SHV-12 CTX-M-15

Carbapenemasen



Thalhammer F. https://www.universimed.com/ch/article/infektiologie/behandlung-multiresistenter-enterobakterien-2104895; abgerufen am 10.08.2022

Carbapenem-Resistenz
das führende Problem



CDC. https://www.cdc.gov/drugresistance/pdf/threats-report/; abgerufen am 10.04.2021

JAMA | Original Investigation

Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance

A Randomized Clinical Trial

Merino-Trial

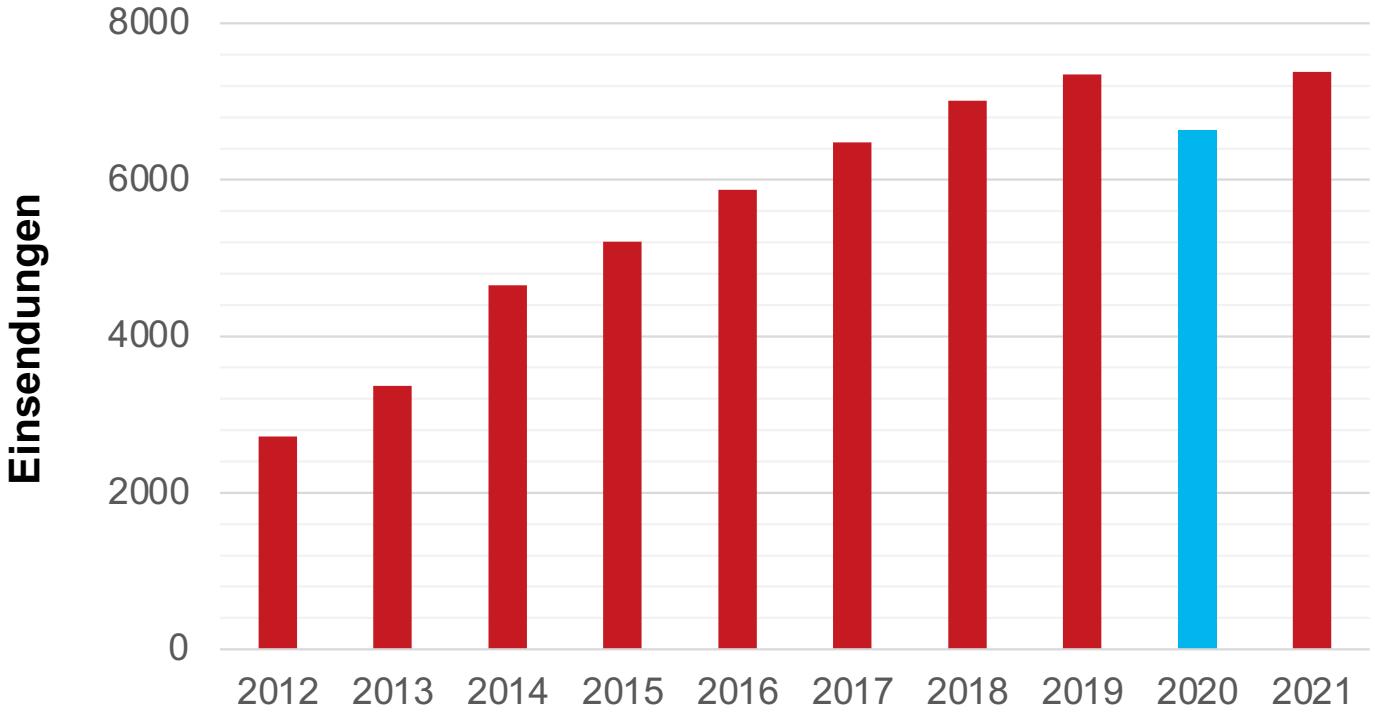
Antibiotikum	
Ampicillin/Sulbactam	R
Piperacillin/Tazobactam	S/I
Ceftriaxon	R
Meropenem	S

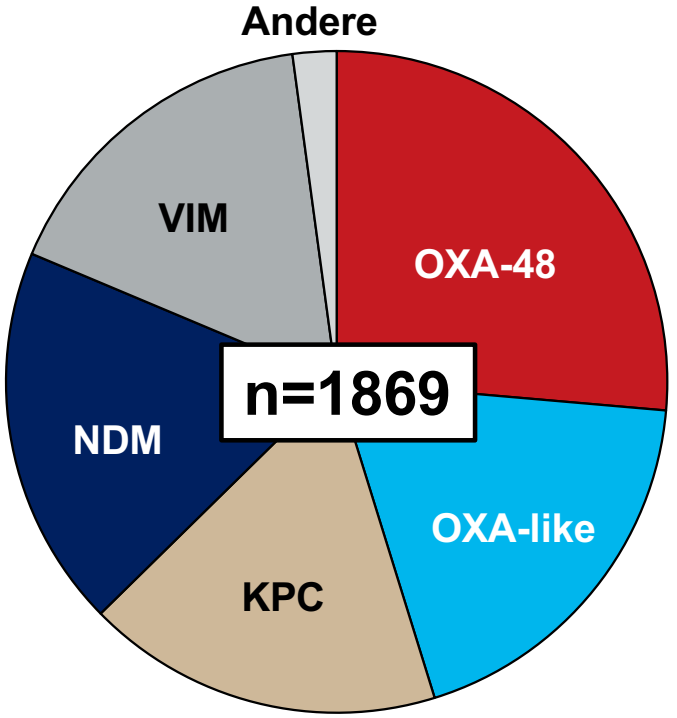
Table 2. Primary Analysis and Subgroup Analyses

	30-d Mortality, No./Total No. (%)		Risk Difference, % (1-Sided 97.5% CI)[a]	*P* Value for Noninferiority
	Piperacillin-Tazobactam	Meropenem		
Primary analysis	23/187 (12.3)	7/191 (3.7)	8.6 (−∞ to 14.5)	.90
Per-protocol analysis	18/170 (10.6)	7/186 (3.8)	6.8 (−∞ to 12.8)	.76
Subgroup analyses[b]				*P* Value for Interaction
OECD country income				
Middle income	8/37 (21.6)	1/35 (2.9)	18.8 (−∞ to 35.0)	.31
High income	15/150 (10.0)	6/156 (3.9)	6.2 (−∞ to 12.5)	
Pitt score				
≥4	5/18 (27.8)	0/9	27.8 (−∞ to 51.3)	.99
<4	18/169 (10.7)	7/182 (3.9)	6.8 (−∞ to 12.8)	
Infecting species				
E coli	17/161 (10.6)	7/166 (4.2)	6.3 (−∞ to 12.6)	.99
K pneumoniae	6/26 (23.1)	0/25	23.1 (−∞ to 42.3)	
Infection				
HAI	18/107 (16.8)	4/107 (3.7)	13.1 (−∞ to 21.8)	.26
Non-HAI	5/80 (6.3)	3/84 (3.6)	2.7 (−∞ to 10.7)	
Appropriate empirical antibiotic therapy				
Appropriate	18/126 (14.3)	5/127 (3.9)	10.3 (−∞ to 18.0)	.70
Inappropriate	5/61 (8.2)	2/64 (3.1)	5.1 (−∞ to 15.2)	
UT vs non-UT source				
UT	7/102 (6.9)	4/128 (3.1)	3.7 (−∞ to 10.7)	.44
Non-UT	16/85 (18.8)	3/63 (4.8)	14.1 (−∞ to 24.5)	
Immune compromise[c]				
Present	10/51 (19.6)	1/40 (2.5)	17.1 (−∞ to 30.5)	.27
Absent	13/136 (9.6)	6/151 (4.0)	5.6 (−∞ to 12.2)	

Harris PNA, et al. JAMA. 2018;320(10):984-994.

Carbapenem-resistente Enterobacterales
in Deutschland (NRZ Bochum 2021)





Pfennigwerth et al. P0617, ECCMID 2022; RKI Epidemiol Bull 2022.

Once upon a time…
… on ICU

Material: Abstrich tief (entnommen) von:,Abdomen
Anforderung: Allgemeine Bakteriologie, Sprosspilze

Ergebnisliste

Kulturelle Ergebnisse

Pseudomonas aeruginosa : in geringer Keimzahl (+)
Nachtestung Cefiderocol: 18 (mm)
Bei dem Isolat wurden erhöhte Carbapenem-MHKs gemessen. Durch spezielle phänotypische bzw. molekularbiologische Tests konnte eine Carbapenemase nachgewiesen werden.
Beurteilung:

NACHWEIS einer Carbapenemase.
Es handelt sich um eine Metallo-Betalaktamase vom Typ VIM-2.

Nach §7 Abs. 2 IfSG sind in §7 nicht genannte Krankheitserreger zu melden, deren örtliche und zeitliche Häufung auf eine schwerwiegende Gefahr für die Allgemeinheit hinweist. Aus fachlicher Sicht spricht viel dafür, dass der Nachweis von Carbapenemasen meldefplichtig ist. Wir haben den Befund daher an das zuständige Gesundheitsamt gemeldet.
4MRGN (MultiResistente GramNegative Erreger)!
Es sollten Hygienemaßnahmen eingeleitet werden entsprechend den KRINKO-Empfehlungen "Hygienemaßnahmen bei Infektionen oder Besiedlung mit multiresistenten gramnegativen Stäbchen".
Die KRINKO empfiehlt eine Isolierung des Patienten.
Rücksprache mit der Krankenhaushygiene empfohlen!
MHK Colistin: 2 mg/l
Bewertung bei inhalativer Therapie: wahrscheinlich auch bei höherer MHK noch wirksam!
MHK Gentamicin: >8 mg/l
MHK Tobramycin: >8 mg/l
MHK Ceftolozan/Tazobactam: >256 mg/l
MHK Ceftazidim/Avibactam: >256 mg/l

Antibiogramme MHK zeigen/verbergen

Wenn die Antibiogramme die Angabe "I" enthalten, bedeutet das "Sensibel bei erhöhter Exposition", das weist darauf hin, dass typisch eine höhere Dosis zu wählen ist. Keinesfalls bedeutet es schlechtere Wirksamkeit.
Link zur vollständigen Erklärung

S sensibel | I sensibel bei erhöhter Exposition/Dosis | R resistent

Antibiotikum	Pseudomonas aeruginosa	
	Bew.	MHK
Piperacillin	R	>64
Piperacillin/Tazobactam	R	>64
Ceftazidim	R	>32
Cefepim	R	>32
Ceftolozan/Tazobactam	R	>256
Ceftazidim/Avibactam	R	>256
Aztreonam	R	>32
Imipenem	R	>8
Meropenem	R	>8
Gentamicin	.	>8
Tobramycin	.	>8
Ciprofloxacin	R	>2
Colistin	S	2

Link zu den Dosierungen, die S/I zugrunde liegen

Andere Ergebnisse

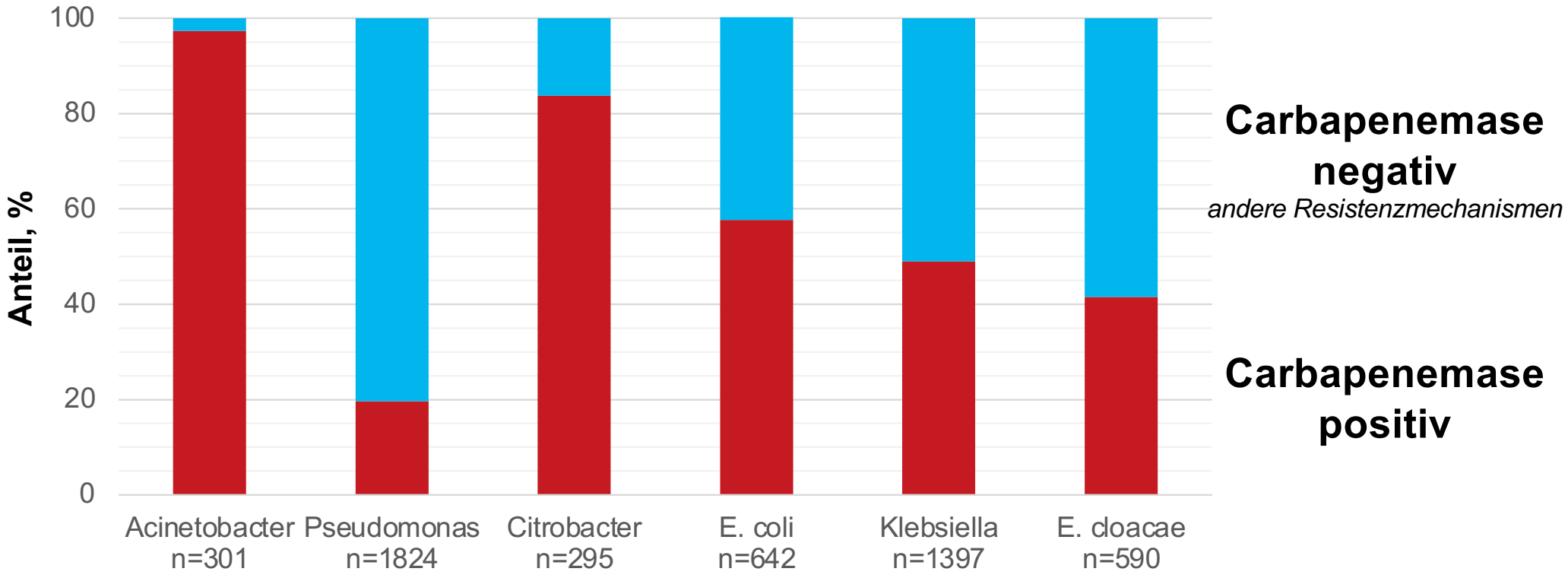
Stammtyp. Ps. aeruginosa : typ-01781: psae_207-3

Befundbeurteilungen/Kommentare:

Sprosspilze nicht nachgewiesen
Der 4-MRGN-Befund wurde am 17.07.20 um 10:02 Uhr von Kristina Ravasz telefonisch mitgeteilt an die behandelnde Ärztin.
Aerobe und anaerobe Kultur abgeschlossen.

Quelle: Eigene Daten.

Carbapenemasen bei gramnegativen Erregern in Deutschland (NRZ Bochum 2021)



Pfennigwerth et al. P0617, ECCMID 2022; RKI Epidemiol Bull 2022.

Carbapenemasen in Deutschland
bei Carbapenem-resistenten Erregern

	Anzahl der getesteten Isolate	Anteil der Carbapenemase-produzierenden Isolate
Enterobacterales	4.161	1.960 (47,1 %)
E. coli	832	538 (64,7 %)
K. pneumoniae	1.590	800 (50,3 %)
E. cloacae	629	244 (38,8 %)
K. aerogenes	422	13 (3,1 %)
andere *Enterobacterales*	688	365 (53,1 %)
P. aeruginosa	1.884	354 (18,8 %)
A. baumannii	479	460 (96,0 %)

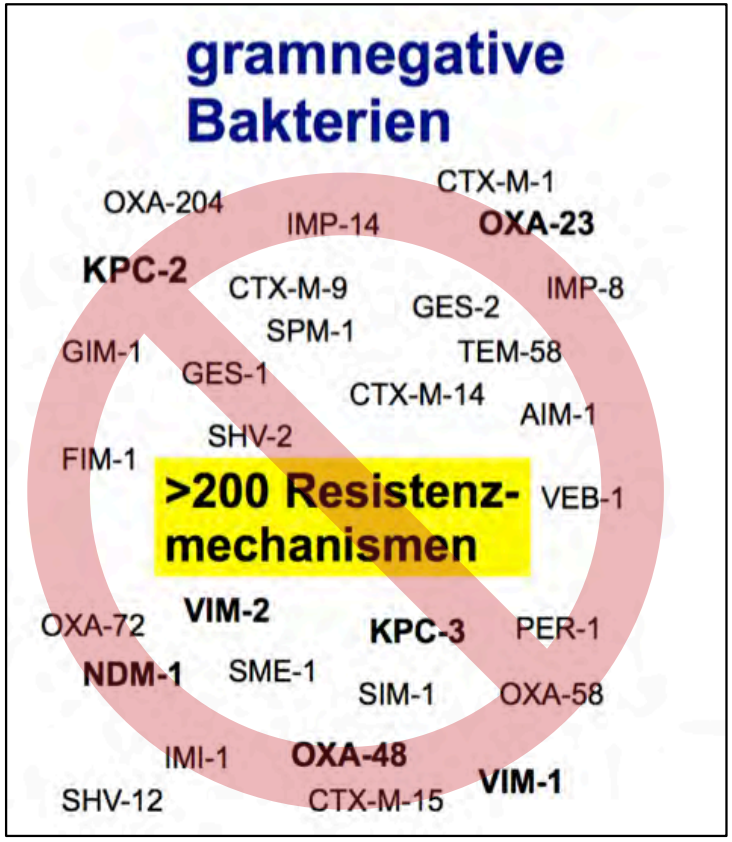
Acinetobacter spp.
→ Cephalosporinasen + Porin-Verlust
→ Carbapenemasen

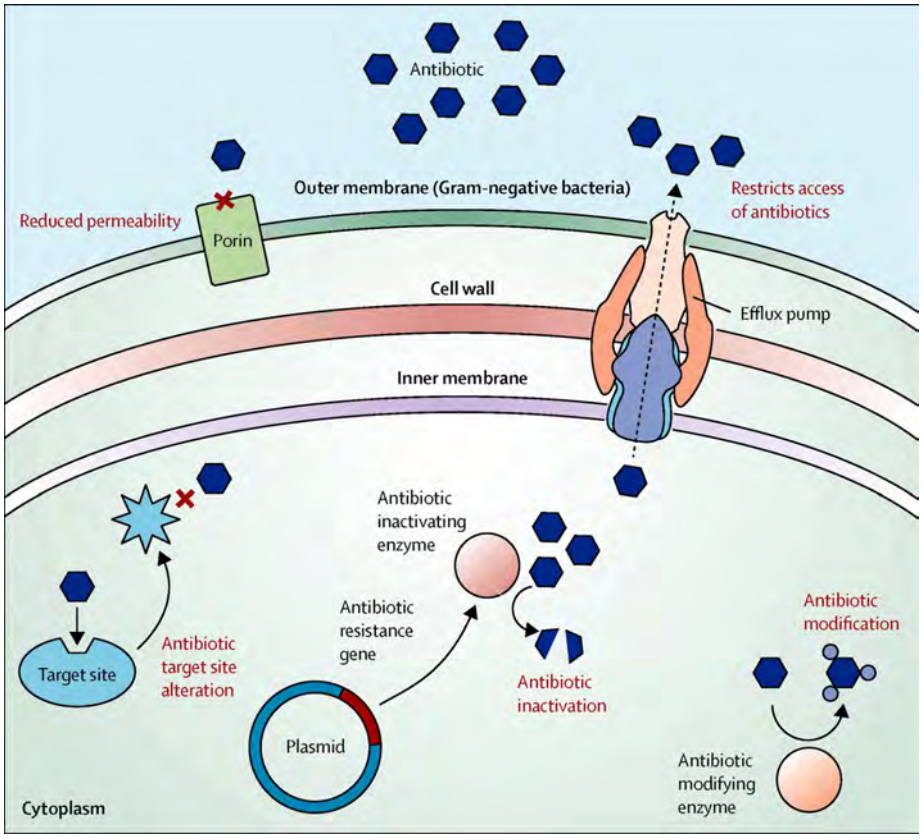
Enterobacterales
→ Cephalosporinasen + Porin-Verlust
→ Carbapenemasen

Pseudomonas aeruginosa
→ Porin-Verlust
→ Efflux-Pumpen
→ *Carbapenemasen (nur ca. 20%)*

Pfennigwerth N. Epidemiologisches Bulletin 2020;29:3-11.

Resistenzmechanismen
mal etwas anschaulicher





Sherrard LJ, et al. Lancet. 2014 Aug 23;384(9944):703-13.

Wirkspektrum MRE-relevanter Antibiotika

Table 2. Spectrum of activity of new antibiotics for difficult-to-treat resistance (DTR) gram-negative bacteria (GNB).

	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	🔴	🔴	🔴	🔴	🟢	🔴

🔴 No activity or intrinsic or acquired resistance. 🟢 Activity. Abbreviations: BL/BLI, β-lactam/β-lactamase Inhibitor CRE, carbapenem resistant Enterobacteriacae; ESBL, extended-spectrum beta-lactamase; MBLs, metallo-β-lactamases; OMPTA, outer membrane protein targeting antibiotics. 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 M, et al. Antibiotics (Basel). 2020 Sep 22;9(9):632.

ß-Lactamase-Inhibitoren
Übersicht

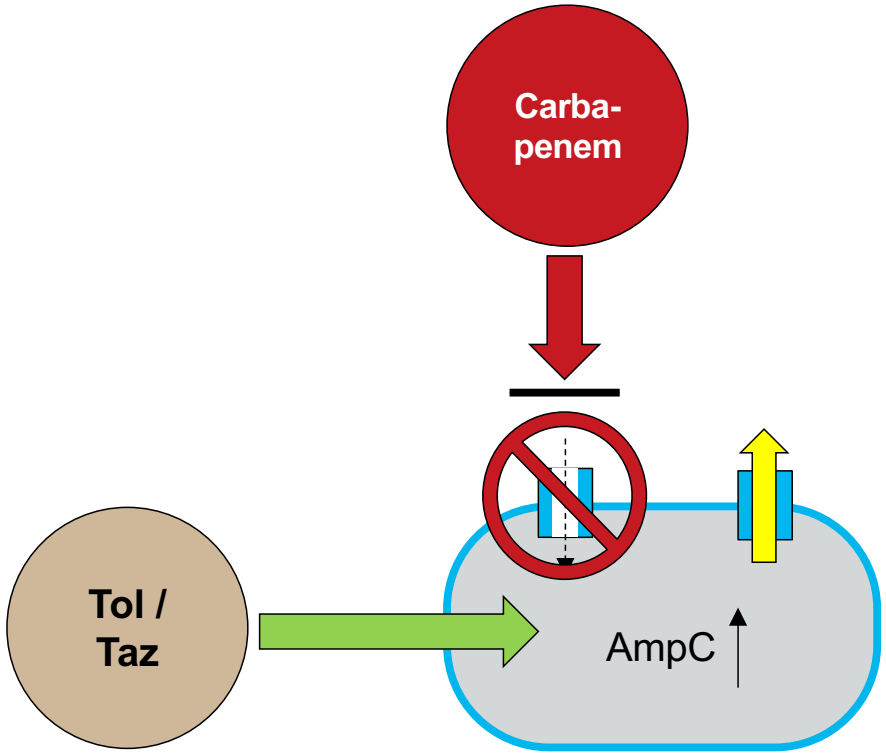
Table 2 | **Comparison of β-lactamase inhibitors**

Structural group	Inhibitor	β-Lactam partner	Development stage (trade name)	Spectrum of inhibition				
				ESBL	AmpC	KPC	OXA-48	MBL
Clavam	Clavulanic acid	• Amoxicillin • Ticarcillin	• Approved (Augmentin) • Approved (Timentin)	✓	–	–	–	–
Penicillanic acid sulfone	Sulbactam	Ampicillin	Approved (Unasyn)	✓	–	–	–	–
	Tazobactam	• Piperacillin • Cefepime • Ceftolozane	• Approved (Zosyn/Tazocin) • Approved outside the US • Approved (Zerbaxa)	✓	–	–	–	–
	Enmetazobactam	Cefepime	Phase II	✓	–	–	–	–
DBO	Avibactam	Ceftazidime	Approved (Avycaz/ Zavicefta)	✓	✓	✓	✓	
		Aztreonam	Phase III	✓	✓	✓	✓	✓
	Relebactam	Imipenem	Approved (Recabrio)	✓	✓	✓	–	–
	Nacubactam	Meropenem	Phase I	✓	✓	✓	–	–
	Zidebactam	Cefepime	Phase I	✓	✓	✓	–	–
	ETX2514	Sulbactam	Phase II	✓	✓	✓	✓	–
Boronic acid	Vaborbactam	Meropenem	Approved (Vabomere)	✓	✓	✓	–	–
	VNRX-5133	Cefepime	Phase I	✓	✓	✓	✓	✓
Pyridine-2-carboxylic acid	ANT431	Meropenem	Preclinical	–	–	–	–	✓

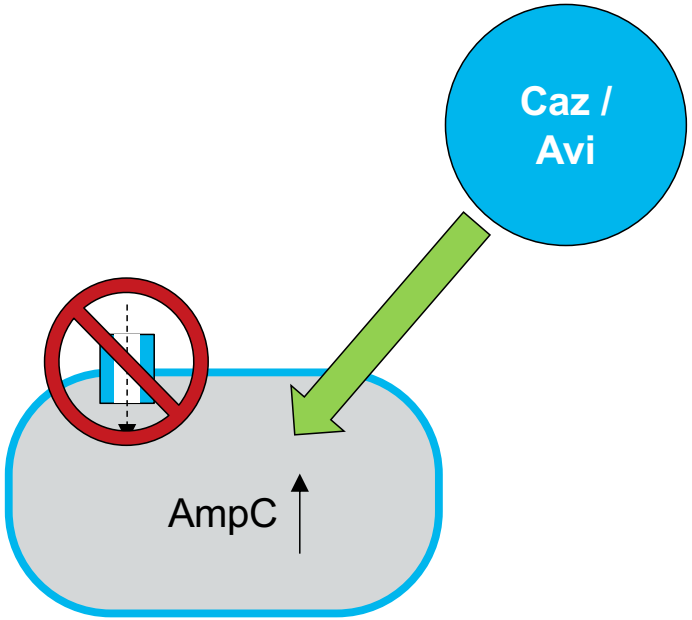
✓, useful inhibitory activity shown; –, no useful inhibitory activity shown; DBO, diazabicyclooctanone analogue; ESBL, extended-spectrum β-lactamase; MBL, metallo-β-lactamase.

Bush K and Bradford PA. Nat Rev Microbiol. 2019;17(5):295-306.

Wirkmechanismus gegen CR-Pseudomonas
Caz/Avi, Imi/Rel & Tol/Taz



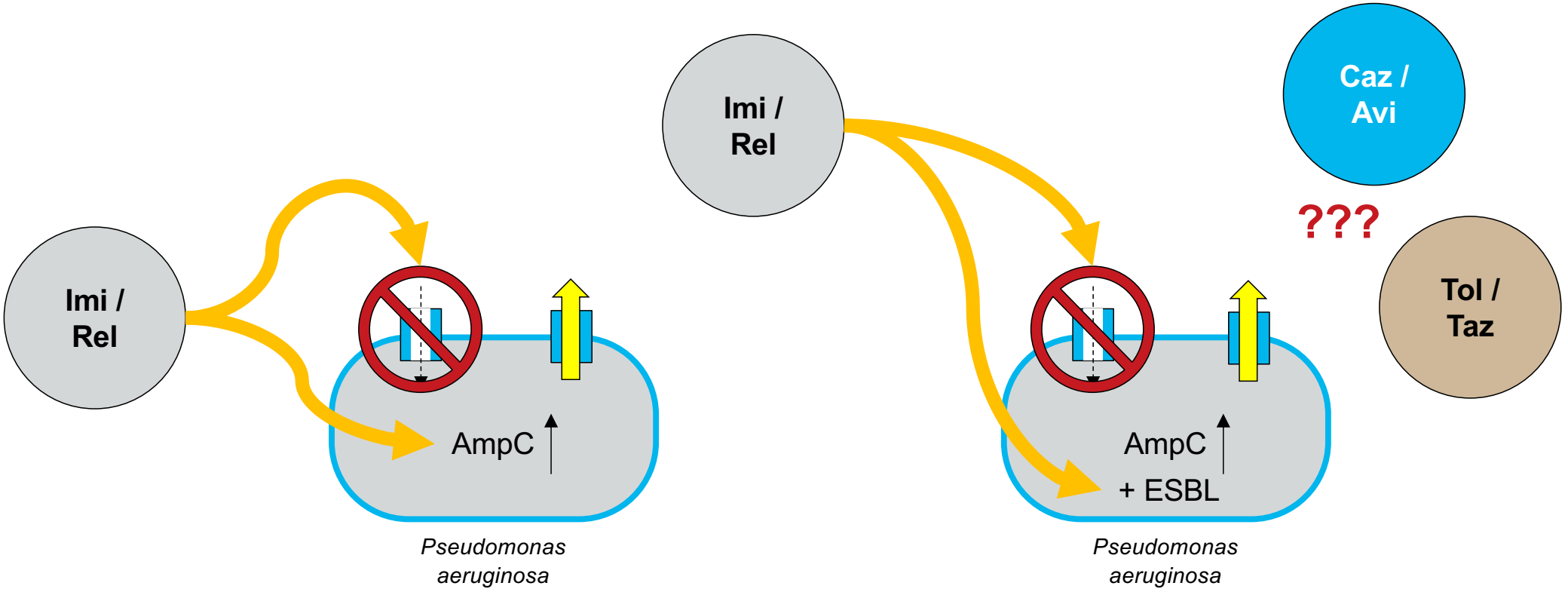
Pseudomonas aeruginosa



Pseudomonas aeruginosa

Mushtaq S, et al. J Antimicrob Chemother. 2021 Jan 19;76(2):434-442.

Wirkmechanismus gegen CR-Pseudomonas
Caz/Avi, Imi/Rel & Tol/Taz



Mushtaq S, et al. J Antimicrob Chemother. 2021 Jan 19;76(2):434-442.

Imipenem/Cilastatin/Relebactam
Zulassungsstudien

Clinical Infectious Diseases
MAJOR ARTICLE

RESTORE-IMI 1: A Multicenter, Randomized, Double-blind Trial Comparing Efficacy and Safety of Imipenem/Relebactam vs Colistin Plus Imipenem in Patients With Imipenem-nonsusceptible Bacterial Infections

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Table 2. Primary and Secondary Prospective Efficacy Endpoints (in the Modified Microbiologic Intent-to-Treat Population) and Secondary Prospective Safety Endpoints (in the Safety Population)

	IMI/REL (n = 21)		Colistin + IMI (n = 10)		Unadjusted Difference	Adjusted Difference[a]	
Endpoint	n	% (95% CI)[b]	n	% (95% CI)[a]	%	%	90% CI
Primary endpoint							
Favorable overall response[c]	15	71.4 (49.8, 86.4)	7	70.0 (39.2, 89.7)	1.4	−7.3	(−27.5, 21.4)
Hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia	7/8	87.5 (50.8, 99.9)	2/3	66.7		20.8	
Complicated intraabdominal infection	0/2[d]	0.0	0/2[e]	0.0		0.0	
Complicated urinary tract infection	8/11	72.7 (42.9, 90.8)	5/5	100.0 (51.1, 100.0)		−27.3 (−52.8, 12.8)	
Secondary endpoints							
Favorable clinical response (day 28)	15[f]	71.4 (49.8, 86.4)	4[g]	40.0 (16.7, 68.8)	31.4	26.3	(1.3, 51.5)
28-day all-cause mortality	2	9.5 (1.4, 30.1)	3	30.0 (10.3, 60.8)	−20.5	−17.3	(−46.4, 6.7)
Treatment-emergent nephrotoxicity[h]	3/29	10.3 (2.8, 27.2)	9/16	56.3 (33.2, 76.9)		−45.9 (−69.1, −18.4)	

Clinical Infectious Diseases
MAJOR ARTICLE

A Randomized, Double-blind, Multicenter Trial Comparing Efficacy and Safety of Imipenem/Cilastatin/Relebactam Versus Piperacillin/Tazobactam in Adults With Hospital-acquired or Ventilator-associated Bacterial Pneumonia (RESTORE-IMI 2 Study)

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Table 2. Primary, Key Secondary, and Other Prespecified Secondary Efficacy Endpoints

Endpoint	IMI/REL, no./No. (%)[a]	PIP/TAZ, no./No. (%)[a]	Adjusted Difference[b], % (95% CI)
Primary endpoint			
Day 28 all-cause mortality (MITT)	42/264 (15.9)	57/267 (21.3)	−5.3 (−11.9 to 1.2)[c]
Key secondary endpoint			
Favorable clinical response at EFU (MITT)	161/264 (61.0)[d]	149/267 (55.8)[d]	5.0 (−3.2 to 13.2)[e]
Other secondary endpoints			
Day 28 all-cause mortality (mMITT)	36/215 (16.7)	44/218 (20.2)	−3.5 (−10.9 to 3.6)
Favorable microbiologic response at EFU (mMITT)	146/215 (67.9)[d]	135/218 (61.9)[d]	6.2 (−2.7 to 15.0)
Favorable clinical response at EFU (CE)	101/136 (74.3)	100/126 (79.4)	−3.7 (−13.6 to 6.4)

Motsch J, et al. Clin Infect Dis. 2020 Apr 15;70(9):1799-1808.
Titov I, et al. Clin Infect Dis. 2021 Dec 6;73(11):e4539-e4548.

Real World Evidence
Imipenem/Cilastatin/Relebactam

Studiendesign: multizentrische, retrospektive, beobachtende Fallserie von hospitalisierten Patienten, die mit Imipenem-Cilastatin-Relebactam (IMI/REL) für ≥ 48 Stunden behandelt wurden

Studienkohorte: 21 Patienten in 8 medizinischen Zentren in 6 Bundesstaaten in den USA zwischen Januar 2020 und August 2021

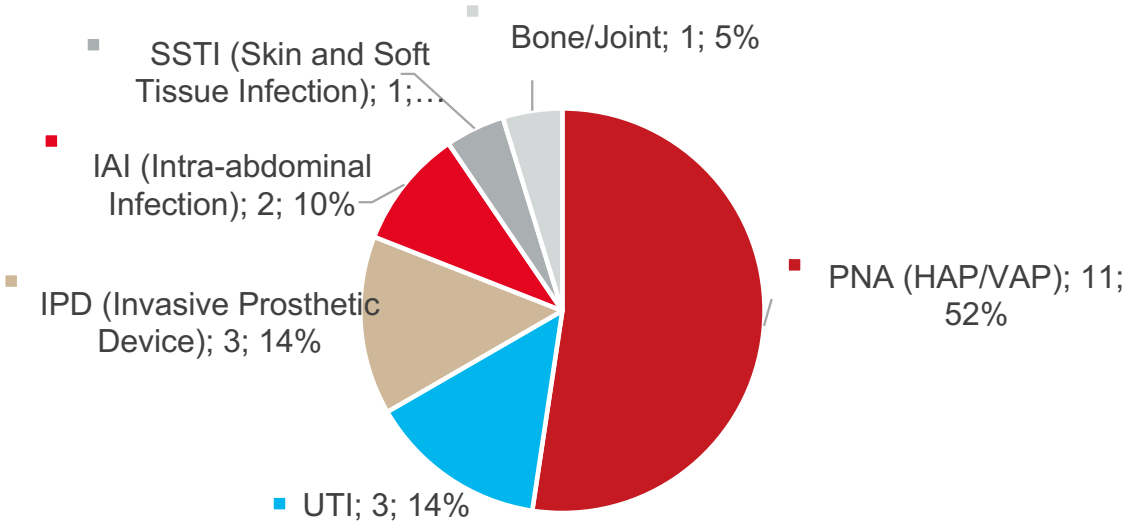
Primärer Endpunkt: 30-Tage-Mortalität aller Ursachen, bewertet 30 Tage nach dem Erhebungsdatum der Indexkultur

Sekundäre Endpunkte: u.a. Klinische Heilung (7 Tage), Mikrobiologisches Rezidiv (30 Tage)

Rebold N, et al. Open Forum Infect Dis. 2021 Dec 9;8(12).

Real World Evidence
Imipenem/Cilastatin/Relebactam

Infektionsquellen



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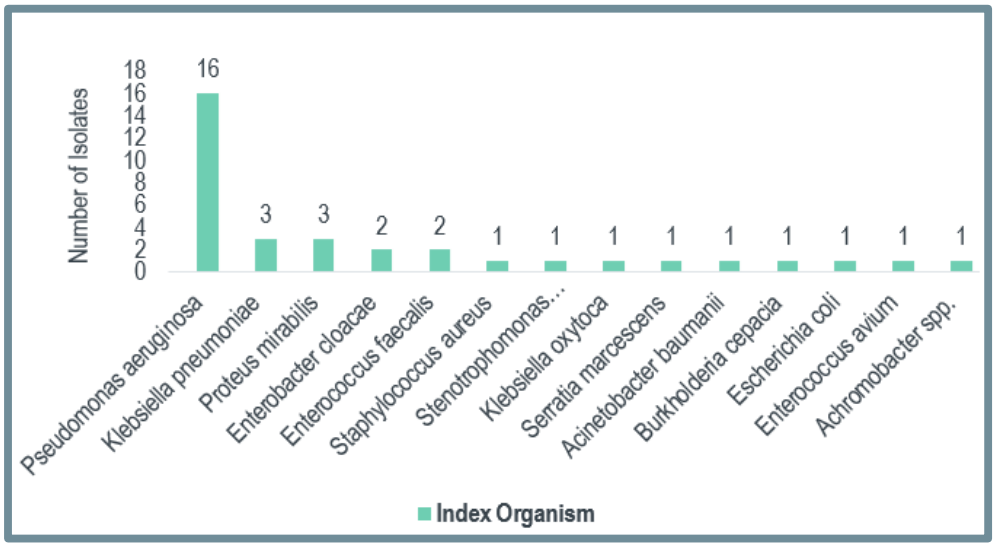
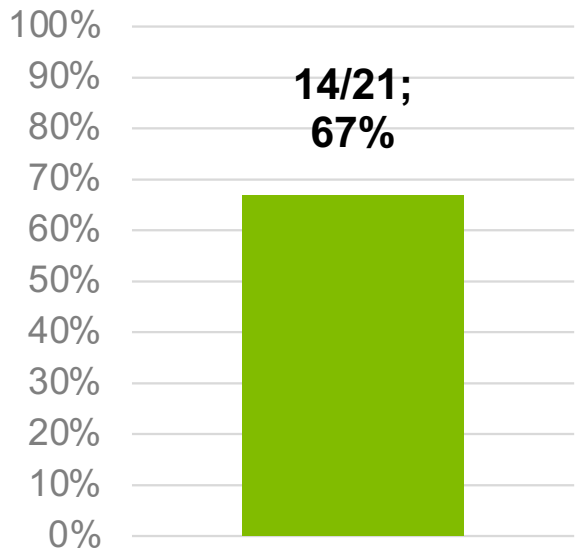


29% der Patienten hatten eine Bakteriämie

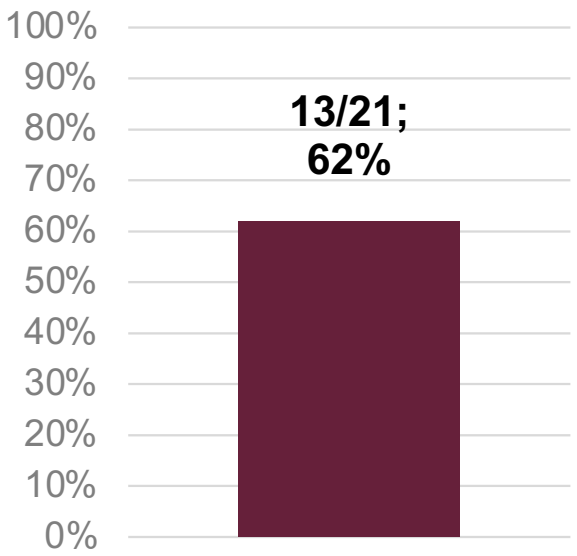
Rebold N, et al. Open Forum Infect Dis. 2021 Dec 9;8(12).

Real World Evidence
Imipenem/Cilastatin/Relebactam

30-Day Survival



Clinical Cure



Rebold N, et al. Open Forum Infect Dis. 2021 Dec 9;8(12).

Real World Evidence
Ceftazidim/Avibactam

Table 1. Demographic and Clinical Characteristics

Characteristics	Total Cohort[a] N = 203	CRE Infection[a] N = 117	*Pseudomonas* spp Infection[a] N = 63
Age, years	62 (49–72)	63 (52–73)	62 (43–74)
Age ≥65 years	90 (44.3)	53 (45.3)	28 (44.4)
Male gender	39 (61.9)	63 (53.8)	39 (61.9)
Race			
African American	93 (45.8)	57 (48.7)	30 (47.6)
White	79 (38.9)	41 (35.0)	21 (33.3)
Latino	8 (3.9)	6 (5.1)	3 (4.8)
Other	22 (10.8)	13 (11.1)	9 (14.3)
BMI	27 (22–35)	27 (22–34)	25 (21–35)
Obese (BMI ≥30 kg/m^2)	77 (37.9)	40 (34.2)	23 (36.5)
Estimated CrCl (mL/min)[b]	65 (34–105)	60 (29–101)	13 (20.6)
CrCl ≤30 mL/min	40 (19.7)	25 (21.4)	10 (15.9)
CrCl 31–50 mL/min	28 (13.8)	14 (12.0)	15 (23.8)
CrCl 51–90 mL/min	50 (24.6)	27 (23.1)	7 (11.1)
CrCl 91–130 mL/min	28 (13.8)	18 (15.4)	11 (17.5)
CrCl >130 mL/min	27 (13.3)	13 (11.1)	7 (11.1)
Hemodialysis	30 (14.8)	20 (17.1)	
Residence Before Admission			
Community	101 (49.8)	59 (50.4)	25 (39.7)
SNF/LTAC	65 (32.0)	38 (32.5)	23 (11.3)
Transferred from outside	28 (13.8)	14 (12.0)	11 (5.4)
Hospital	9 (4.4)	6 (3.0)	4 (2.0)
Other			
Comorbid Conditions			
Diabetes	85 (41.9)	46 (39.3)	33 (52.4)
Heart failure	37 (18.2)	20 (17.1)	12 (19.0)
Chronic kidney disease	65 (32.0)	40 (34.2)	19 (30.2)
Chronic lung disease	74 (36.5)	40 (34.2)	29 (46.0)
Malignancy	27 (13.3)	19 (16.2)	6 (9.5)
Liver disease	21 (10.3)	15 (12.8)	2 (3.2)
Charlson comorbidity score	4 (2–6)	4 (2–7)	4 (2–6)
Charlson comorbidity score > 4	85 (41.9)	51 (43.6)	25 (39.7)
Immunocompromised	22 (10.8)	16 (13.7)	4 (6.3)
MDRO infection or colonization within 1 year	97 (47.8)	56 (47.9)	34 (54.0)
Recent antibiotic exposure (≥24 hours within 90 days)	157 (77.3)	96 (82.1)	51 (81.0)
Recent hospitalization (≥48 hours within 90 days)	151 (74.4)	94 (80.3)	46 (73.0)
Recent surgery (within 30 days)	38 (18.7)	23 (19.7)	10 (15.9)
ICU at index culture	102 (50.2)	62 (53.0)	35 (55.6)
SOFA score	5 (2–8)	5 (2–8)	5 (2–9)

Open Forum Infectious Diseases

MAJOR ARTICLE

Real-World Experience With Ceftazidime-Avibactam for Multidrug-Resistant Gram-Negative Bacterial Infections

- Multizentrische, retrospektive Kohortenstudie an 6 Zentren in den USA zwischen 2015 und 2019
- Eingeschlossen wurden erwachsene Patienten die Caz/Avi über ≥ 72 Stunden erhalten haben
- **Primärer Endpunkt:** Klinisches Therapieversagen, definiert als „composite“ der 30-Tage Gesamtmortalität, dem 30-Tage mikrobiologisches Therapieversagen, und/oder der fehlenden klinischen Verbesserung der Infektion

Jorgensen SCJ, et al. Open Forum Infect Dis. 2019 Dec 6;6(12):ofz522.

Real World Evidence
Ceftazidim/Avibactam

Table 4. Outcomes

Outcome	Total Cohort[a] N = 203	CRE Infection[a] N = 117	*Pseudomonas* spp Infection[a] N = 63
Effectiveness			
Discharge Disposition			
Home	57 (28.1)	31 (26.5)	16 (25.4)
SNF/LTAC	90 (44.3)	53 (45.3)	32 (50.8)
Inpatient rehabilitation facility	14 (6.9)	8 (6.8)	3 (4.8)
Hospice	8 (3.9)	5 (4.3)	2 (3.2)
Inhospital mortality	34 (16.7)	20 (17.1)	10 (15.9)
Discharge Disposition Among Patients Admitted From Home			
Home	47/101 (46.5)	25/59 (42.4)	11/25 (44.0)
SNF/LTAC	29/101 (28.7)	18/59 (30.5)	9/25 (36.0)
Inpatient rehabilitation facility	10/101 (9.9)	6/59 (10.2)	3/25 (12.0)
Hospice	2/101 (2.0)	2/59 (3.4)	0
Inhospital mortality	13/101 (12.9)	8/59 (13.6)	2/25 (8.0)
Composite clinical failure	59 (29.1)	34 (29.1)	19 (30.2)
30-day mortality	35 (17.2)	19 (16.2)	11 (17.5)
30-day recurrence	12 (5.9)	7 (6.0)	4 (6.3)
Worsen or failure to improve while on CZA	32 (15.8)	18 (15.4)	12 (19.0)
Development of CZA resistance (n = 61)[b]	0	0	0
Safety			
Acute kidney injury[c]	10/177 (5.6)	5/101 (5.0)	4/56 (7.1)
Clostridioides difficile infection	3 (1.5)	3 (2.6)	0
Rash	2 (1.0)	0	2 (3.2)

Jorgensen SCJ, et al. Open Forum Infect Dis. 2019 Dec 6;6(12):ofz522.

Real World Evidence
Ceftolozan/Tazobactam

RESEARCH Open Access

Real-world use of ceftolozane/tazobactam: a systematic literature review

Laura Puzniak[1*], Ryan Dillon[1], Thomas Palmer[2], Hannah Collings[2] and Ashley Enstone[2]

Abstract

Background: Antibacterial-resistant gram-negative infections are a serious risk to global public health. Resistant Enterobacterales and *Pseudomonas aeruginosa* are highly prevalent, particularly in healthcare settings, and there are limited effective treatment options. Patients with infections caused by resistant pathogens have considerably worse outcomes, and incur significantly higher costs, relative to patients with susceptible infections. Ceftolozane/tazobactam (C/T) has established efficacy in clinical trials. This review aimed to collate data on C/T use in clinical practice.

Methods: This systematic literature review searched online biomedical databases for real-world studies of C/T for gram-negative infections up to June 2020. Relevant study, patient, and treatment characteristics, microbiology, and efficacy outcomes were captured.

Results: There were 83 studies comprising 3,701 patients were identified. The most common infections were respiratory infections (52.9% of reported infections), urinary tract infections (UTIs; 14.9%), and intra-abdominal infections (IAIs; 10.1%). Most patients included were seriously ill and had multiple comorbidities. The majority of patients had infections caused by *P. aeruginosa* (90.7%), of which 86.0% were antimicrobial-resistant. C/T was used as both a 1.5 g q8h and 3 g q8h dose, for a median duration of 7–56 days (varying between studies). Outcome rates were comparable between studies: clinical success rates ranged from 45.7 to 100.0%, with 27 studies (69%) reporting clinical success rates of > 70%; microbiological success rates ranged from 31 to 100%, with 14 studies (74%) reporting microbiological success rates of > 70%. Mortality rates ranged from 0 to 50%, with 31 studies (69%) reporting mortality rates of ≤ 20%. In comparative studies, C/T was as effective as aminoglycoside- or polymyxin-based regimens, and in some instances, significantly more effective.

Conclusions: The studies identified in this review demonstrate that C/T is effective in clinical practice, despite the diverse group of seriously ill patients, different levels of resistance of the pathogens treated, and varying dosing regimens used. Furthermore, comparative studies suggest that C/T offers a successful alternative to standard of care (SoC).

Keywords: Ceftolozane/tazobactam, *Pseudomonas aeruginosa*, Antibacterial resistance, Real-world evidence

- Studien bis zum Jahr 2020 in der Analyse enthalten
- 83 Studien weltweit
- 3701 Patienten mit Ceftolozan/Tazobactam
- Häufigste Indikationen: Respiratory (52,9%); UTI (14,9 %); Intraabdominell (10,1%)
- Erreger: P. aeruginosa (90,7%), davon 86 % MDR oder XDR
- Dosierung: 1,5g oder 3,0g C/T alle 8 Stunden
- Behandlungsdauer: 7-56 Tage
- Effektivität wie Aminoglykosid- oder Polymyxinbasierte Antibiotika Therapie, teilweise sogar signifikant besser

Puzniak et al. Antimicrob Resist Infect Control (2021) 10:68.

Real World Evidence
Ceftolozan/Tazobactam

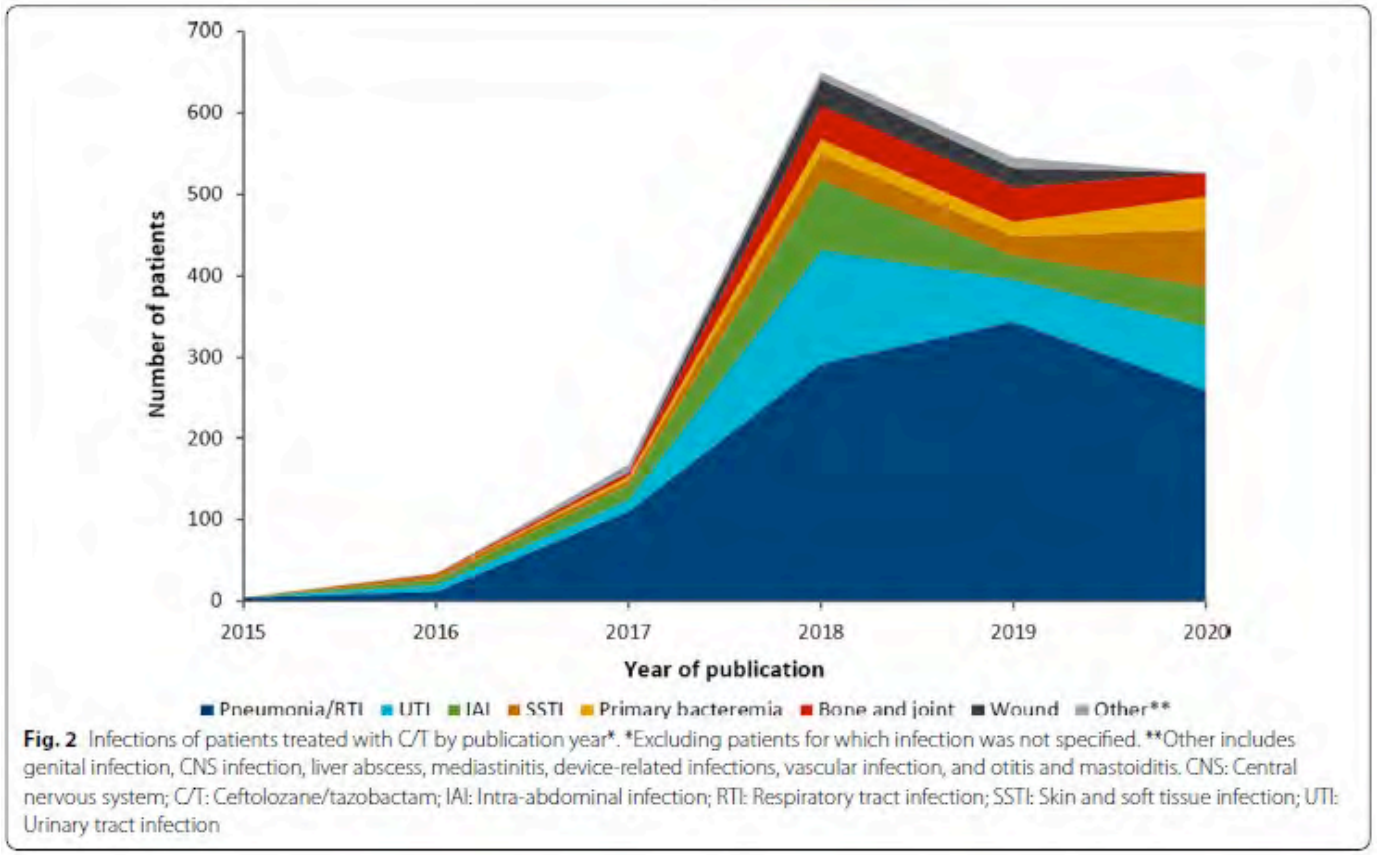


Fig. 2 Infections of patients treated with C/T by publication year*. *Excluding patients for which infection was not specified. **Other includes genital infection, CNS infection, liver abscess, mediastinitis, device-related infections, vascular infection, and otitis and mastoiditis. CNS: Central nervous system; C/T: Ceftolozane/tazobactam; IAI: Intra-abdominal infection; RTI: Respiratory tract infection; SSTI: Skin and soft tissue infection; UTI: Urinary tract infection

Puzniak et al. Antimicrob Resist Infect Control (2021) 10:68.

Real World Evidence
Ceftolozan/Tazobactam

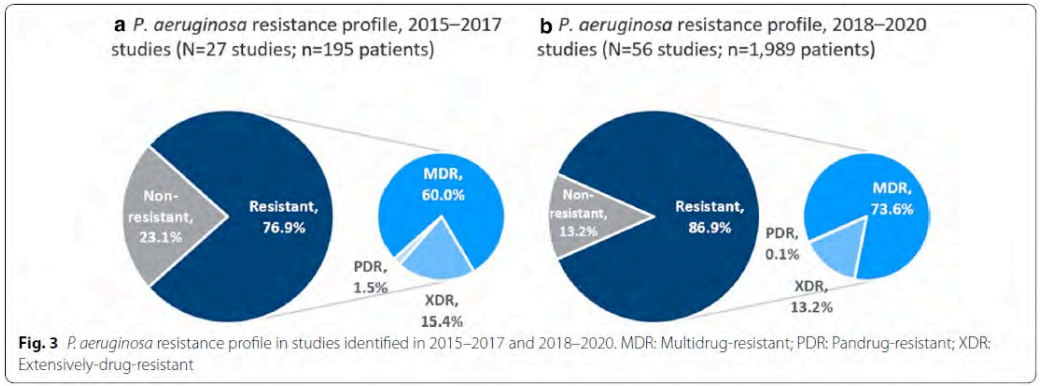


Fig. 3 *P. aeruginosa* resistance profile in studies identified in 2015–2017 and 2018–2020. MDR: Multidrug-resistant; PDR: Pandrug-resistant; XDR: Extensively-drug-resistant

Citation, study design, location	Study design	Patient/infection description	Treatment groups	Outcome description	Outcome, % (n/N)		p-value/aOR
					C/T	Comparator	
Aminoglycoside/polymyxin comparator							
Caffrey et al. 2020 [80] Retrospective, multicenter, cohort US	Cohort	Patients had MDR PsA infections	C/T (N = 57) vs. aminoglycoside/polymyxin-based (N = 155)	Clinical cure	-	-	-
				Mortality, 30-day	17.5 (10/57)	18.1 (28/155)	aOR: 0.78 95% CI: 0.30–2.03
				Mortality, inpatient	15.8 (9/57)	27.7 (43/155)	**aOR: 0.39 95% CI: 0.16–0.93**
				Microbiological cure	31.0 (13/42)	30.6 (33/108)	aOR: 0.88 95% CI: 0.35–2.21
Vena et al. 2020 [23] Retrospective, multicenter, case–control Italy	Case–control	Patients had pneumonia or bacteremia caused by MDR or XDR PsA	C/T (N = 16) vs. aminoglycoside/polymyxin-based (N = 32)	Clinical cure	81.3 (13/16)	56.3 (18/32)	0.11
				Mortality, 30-day	18.8 (3/16)	28.1 (9/32)	0.72
				Microbiological cure	-	-	-
Pogue et al. 2019 [27] Retrospective, multicenter, case–control US	Case–control	Patients had an MDR or XDR PsA infection	C/T (N = 100) vs. aminoglycoside/polymyxin-based (N = 100)	Clinical cure	81.0 (81/100)	61.0 (61/100)	**0.002**
				Mortality, in hospital	20.0 (20/100)	25.0 (25/100)	0.400
				Microbiological cure	-	-	-
Other comparator							
Fernández-Cruz et al. 2019 [26] Retrospective, single center, case–control Spain	Case–control	Patients had hematological malignancies and PsA infection	C/T (N = 19) vs. mixed SoC antibacterial agents (N = 38)	Clinical cure, 14-day	89.5 (17/19)	71.1 (27/38)	0.183
				Mortality, 30-day	5.3 (1/19)	28.9 (11/38)	**0.045**
				Microbiological cure	-	-	-
Mills et al. 2019 [83] Retrospective, multicenter cohort US	Cohort	Patients had pneumonia with an MDR PsA culture	C/T (N = 62) vs. mixed SoC antibacterial agents (N = 53)	Clinical cure, 14-day	72.6 (45/62)	67.9 (36/53)	0.683
				Mortality	29.0 (18/62)	26.4 (14/53)	0.840
				Microbiological cure	-	-	-

Puzniak et al. Antimicrob Resist Infect Control (2021) 10:68.

Real World Evidence bei Neutropenie
Ceftolozan/Tazobactam

AMERICAN SOCIETY FOR MICROBIOLOGY | Microbiology Spectrum

RESEARCH ARTICLE

Real-Life Use of Ceftolozane/Tazobactam for the Treatment of Bloodstream Infection Due to *Pseudomonas aeruginosa* in Neutropenic Hematologic Patients: a Matched Control Study (ZENITH Study)

TABLE 1 Clinical characteristics of patients with *Pseudomonas aeruginosa* bloodstream infection compared by treatment groups

Characteristics[a]	Total $n = 132$ (%)[b]	Cases $n = 44$ (% or IQR)[b]	Controls $n = 88$ (% or IQR)[b]	*P* value
Gender (male)	85 (64.49)	28 (63.6)	57 (64.8)	1.00
Age (yrs, median, IQR)	54 (41–65)	52 (37.2–61.7)	54.5 (41–67.5)	0.68
Comorbidities	47 (35.6)	15 (34.1)	32 (36.4)	0.84
Chronic cardiac disease	18 (13.6)	3 (6.8)	15 (17)	0.17
Diabetes mellitus	11 (8.3)	3 (6.8)	8 (9.1)	0.75
Chronic obstructive pulmonary disease	10 (7.6)	1 (2.3)	9 (10.2)	0.16
Chronic liver disease	7 (5.3)	2 (4.5)	5 (5.7)	1.00
Chronic kidney disease	4 (3)	2 (4.5)	5 (5.7)	0.60
Hematologic malignancy				
Acute myeloid leukemia	67 (50.8)	24 (54.5)	43 (48.9)	0.58
Acute lymphoid leukemia	15 (11.4)	6 (13.6)	9 (10.2)	0.57
Lymphoproliferative disorder	36 (27.3)	10 (22.7)	26 (29.5)	0.53
Chronic lymphocytic leukemia	5 (3.8)	2 (4.5)	3 (3.4)	1.00
Multiple myeloma	5 (3.8)	1 (2.3)	4 (4.5)	0.66
Other	4 (3)	1 (2.3)	3 (3.4)	1.00
Hematopoietic stem cell transplant (HSCT)	49 (37.1)	17 (38.6)	32 (36.4)	0.79
Type of HSCT				
Autologous HSCT	3 (6.2)	0 (0)	3 (9.7)	0.54
Allogeneic HSCT	45 (91.8)	17 (100)	28 (87.5)	0.54
Graft-versus-host disease	14 (32.6)	6 (40)	8 (28.6)	0.50

- Multizentrische, internationale Matched-Cohort-Studie zu Blutstrominfektionen durch P. aeruginosa bei neutropenischen hämatologischen Patienten, die mit C/T behandelt wurden.
- Kontrollgruppe bestand aus Patienten, die mit anderen Antibiotika behandelt wurden.
- 91 % der Fälle wurden durch multiresistente (MDR) Stämme verursacht.
- Häufigste Quellen: Endogene Infektionen (35,6 %), gefolgt von Pneumonie (25,8 %)
- Studienendpunkte: 7-Tage und 30-Tage Gesamtsterblichkeit

Bergas A, et al. Microbiol Spectr. 2022 Jun 29;10(3):e0229221.

Real World Evidence bei Neutropenie

Ceftolozan/Tazobactam

TABLE 2 Therapy regimens by treatment group

Treatment type[a]	Total *n* = 132 (%)	Cases *n* = 44 (%)	Controls *n* = 88 (%)
Empirical treatment			
Monotherapy	66/132 (50)	18/44 (40.9)	48/88 (54.5)
Ceftolozane-tazobactam	4/66 (6)	4/18 (22.2)	0/48 (0)
Piperacilin/tazobactam	23/66 (34.8)	6/18 (33.3)	17/48 (35.4)
Antipseudomonal carbapenems (meropenem/imipenem)	28/66 (42.4)	6/18 (33.3)	22/48 (45.8)
Antipseudomonal cephalosporins (cefepime/ceftazidime)	8/66 (12.1)	2/18 (11.1)	6/48 (12.5)
Others[b]	3/66 (4.5)	0/18 (0)	3/48 (6.2)
Combination therapy	63/132 (47.3)	23/44 (52.3)	40/88 (45.5)
C/T + AG	6/63 (9.5)	6/23 (26.1)	0/40 (0)
C/T + colistin	1/63 (1.6)	1/23 (4.3)	0/40 (0)
Other β-lactam + AG	42/63 (66.7)	13/23 (56.5)	30/40 (75)
Other β-lactam + non-AG	9/63 (14.3)	3/23 (13)	6/40 (15)
Non-β-lactam combination	4/63 (6.3)	0/23 (0)	4/40 (10)
No empirical treatment	3/132 (2.3)	3/44 (6.8)	0/88 (0)
Targeted treatment			
Monotherapy	52/132 (39.4)	17/44 (38.6)	35/88 (39.8)
Ceftolozane-tazobactam	16/52 (30.8)	16/17 (94.1)	0/35 (0)
Piperacilin/tazobactam	8/52 (15.4)	1/17 (5.9)	9/35 (25.7)
Antipseudomonal carbapenems (meropenem, imipenem, doripenem)	7/52 (13.5)	3/17 (0)	10/35 (28.5)
Colistin	8/52 (15.4)	0/17 (0)	8/35 (22.9)
Antipseudomonal cephalosporins (cefepime, ceftazidime)	3/52 (5.8)	0/17 (0)	3/35 (8.5)
Fluoroquinolones	3/52 (5.8)	0/17 (0)	3/35 (8.6)
Amikacin	2/52 (3.8)	0/17 (0)	2/35 (5.7)
Combination therapy (2 antibiotics)	53/132 (40.2)	21/44 (47.7)	32/88 (36.4)
C/T + AG	18/53 (30.1)	14/21 (66.7)	0/32 (0)
C/T + Colistin	5/53 (9.4)	5/21 (23.8)	0/32 (0)
Other β-lactam + AG	19/53 (35.8)	1/21 (4.8)	18/32 (56.2)
β-Lactam + non-AG	8/53 (15.1)	0/21 (0)	8/32 (25)
Non-β-lactam combination	7/53 (13.2)	1/21 (4.8)	6/32 (18.7)
Triple therapy	16/132 (12.1)	6/88 (6.8)[c]	10/88 (11.4)
No treatment	11/132 (8.3)	0/44 (0)	11/88 (12.5)

TABLE 3 Resistance rates to the different antibiotic classes

Antibiotic families	Total *n*/available isolates *n* (%)[a]	Cases *n*/available isolates *n* (%)[a]	Controls *n*/available isolates *n* (%)[a]	*P* value
Cephalosporins	95/129 (73.6)	37/44 (84.1)	58/85 (68.2)	0.053
Cefepime	70/103 (68)	34/39 (87.2)	36/64 (56.3)	0.001
Ceftazidime	78/128 (60.9)	28/43 (65.1)	50/85 (58.8)	0.49
Piperacillin-tazobactam	93/127 (73.2)	35/42 (83.3)	58/85 (68.2)	0.071
Carbapenems	82/128 (64.1)	35/43 (81.4)	47/85 (55.3)	0.004
Imipenem	90/122 (73.8)	35/38 (92.1)	55/84 (65.5)	0.002
Meropenem	82/123 (66.7)	35/41 (85.4)	47/82 (57.3)	0.002
Doripenem	15/19 (78.9)	7/8 (87.5)	8/11 (72.7)	0.60
Aztreonam	59/77 (76.6)	26/28 (92.9)	33/49 (67.3)	0.011
Aminoglycosides	74/109 (67.9)	30/41 (73.2)	44/68 (64.7)	0.35
Gentamycin	65/118 (55.1)	28/41 (68.3)	37/77 (48.1)	0.035
Amikacin	31/121 (25.6)	9/37 (24.3)	22/84 (26.2)	0.82
Tobramycin	56/98 (57.1)	25/39 (64.1)	31/59 (52.5)	0.25
Fluoroquinolones	102/129 (79.1)	40/44 (90.9)	62/85 (72.9)	0.017
Ciprofloxacin	95/127 (74.8)	36/42 (85.7)	59/85 (69.4)	0.036
Levofloxacin	58/74 (78.4)	23/25 (92)	35/49 (71.4)	0.042
Fosfomycin	23/48 (47.9)	7/21 (33.3)	16/27 (59.3)	0.074
Colistin	0/113	0/36	0/77	–[b]

Bergas A, et al. Microbiol Spectr. 2022 Jun 29;10(3):e0229221.

Real World Evidence bei Neutropenie
Ceftolozan/Tazobactam

TABLE 4 Outcomes of 132 patients with *Pseudomonas aeruginosa* bloodstream infection compared by treatment groups

Endpoints[a]	Total *n* = 132 (%)	Cases *n* = 44 (%)	Controls *n* = 88 (%)	*P* value
Primary endpoint				
Seven-day case fatality rate	32 (24.2)	3 (6.8)	29 (34.1)	0.001
Thirty-day case fatality rate	53 (40.2)	10 (22.7)	43 (48.9)	0.005
Secondary endpoints				
Persistent BSI	22 (17.1)	4 (9.1)	18 (21.2)	0.084
ICU admission[b]	46 (34.8)	12 (27.3)	34 (38.6)	0.246
Need for invasive mechanical ventilation[b]	35 (26.7)	6 (13.6)	29 (33.3)	0.021
Other				
Nephrotoxicity	33 (27.9)	8 (18.2)	25 (32.9)	0.082

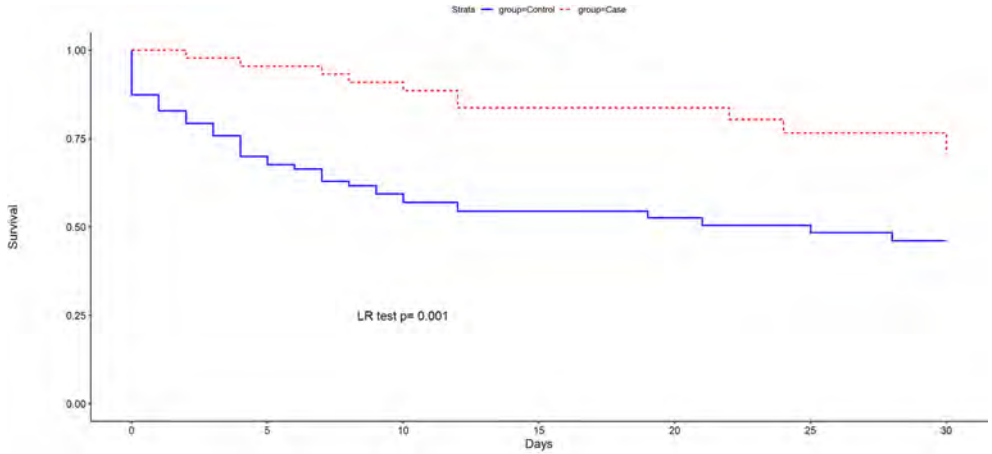


TABLE 5 Univariate and multivariate analysis of factors associated with 7-day case fatality rate

Characteristics	Dead *n* = 32 (%)	Alive *n* = 100 (%)	*P* value	Adjusted OR (95% CI)[a]	*P* value[b]
Male gender	22 (68.8)	63 (63)	0.55	0.67 (0.24–1.90)	0.462
Age (yrs) (median, IQR)	55 (18–79)	54 (18–90)	0.73	0.60 (0.2–1.60)	0.309
Inadequate empirical antibiotic therapy	21 (63.6)	41 (41.4)	0.027	2.73 (1.11–6.68)	**0.028**
Therapy with ceftolozane-tazobactam	3 (9.4)	41 (41)	0.001	0.16 (0.04–0.58)	**0.006**
Persistent bloodstream infection	9 (30)	13 (13.1)	0.031	2.13 (0.73–6.21)	0.16

TABLE 6 Univariate and multivariate analysis of factors associated with 30-day case fatality rate

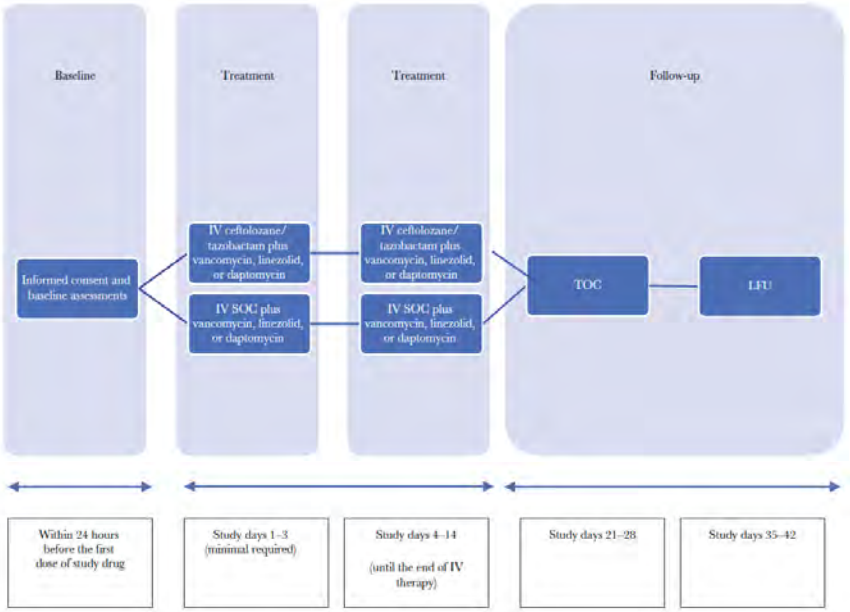
Characteristics[a]	Dead *n* = 53 (%)	Alive *n* = 98 (%)	*P* value	Adjusted OR (95% CI)[a]	*P* value[b]
Female gender	19 (40.4)	28 (59.6)	0.96	0.97 (0.38–2.45)	0.958
Age (yrs) (median, IQR)	53 (18–90)	54.5 (18–79)	0.79	0.98 (0.95–1.00)	0.133
Pneumonia	20 (58.8)	14 (41.2)	0.014	5.45 (1.84–16.13)	**0.002**
Therapy with ceftolozane-tazobactam	10 (22.7)	34 (77.3)	0.004	0.19 (0.07–0.55)	**0.002**
Persistent bloodstream infection	14 (63.6)	8 (36.4)	0.009	5.44 (1.61–18.31)	**0.006**
Infection due to XDR PA	23 (52.3)	21 (47.7)	0.045	1.76 (0.68–4.54)	0.240
Profound neutropenia (<100 cells/mm³)	41 (48.8)	43 (51.2)	0.009	5.49 (1.96–0.15.36)	**0.001**

Bergas A, et al. Microbiol Spectr. 2022 Jun 29;10(3):e0229221.

Real World Evidence bei Neutropenie
Ceftolozan/Tazobactam

Open Forum Infectious Diseases
MAJOR ARTICLE

A Prospective Randomized Study Comparing Ceftolozane/Tazobactam to Standard of Care in the Management of Neutropenia and Fever in Patients With Hematological Malignancies



- Prospektive, randomisierte, Open-label Studie
- C/T Vergleich mit SOC für die empirische Behandlung von Fieber in der Neutropenie bei Patienten mit hämatologischen Malignomen
- 100 Patienten eingeschlossen, die C/T- oder SOC-Antibiotika (Cefepime, Pip/Taz oder Meropenem) in Kombination mit gram-positiven Antibiotika erhielten
- Primäre Endpunkte: Klinischer Erfolg und Sicherheit zum Ende der i.v. Therapie
- Nachbeobachtung bis Tag 42

Chaftari AM, et al. Open Forum Infect Dis. 2022 Feb 14;9(6):ofac079.

Real World Evidence bei Neutropenie
Ceftolozan/Tazobactam

Characteristic	Ceftolozane/ Tazobactam (n = 47)	Standard of Care (n = 50)	*P* Value
Age, y, median (range)	60 (25–84)	55 (18–79)	.12
Sex			.65
Male	28 (60)	32 (64)	
Female	19 (40)	18 (36)	
Race/ethnicity			.85
White	32 (68)	35 (70)	
Black	4 (9)	5 (10)	
Hispanic	6 (13)	7 (14)	
Asian	0 (0)	1 (2)	
Middle Eastern	3 (6)	1 (2)	
Other	2 (4)	1 (2)	
Hematological malignancy			.32
ALL	9 (19)	12 (24)	
AML	19 (40)	22 (44)	
CML	3 (6)	0	
Lymphoma	9 (19)	6 (12)	
Other	7 (15)	10 (20)	
BMT within 1 y prior to fever	6 (13)	9 (18)	.48
Autologous	2/6 (33)	4/9 (44)	
Allogeneic	4/6 (67)	5/9 (56)	
Type of allogeneic transplant			
Matched unrelated donor	0	1/5 (20)	
HLA matched related donor	4/4 (100)	4/5 (80)	
GVHD	1/6 (17)	1/8 (13)	>.99
Temperature at baseline, °C, median (IQR)	37.3 (36.9–38.2)	37.5 (37.0–38.3)	.31
Temperature at initial presentation, °C			.32
<36	0	0	
36–38	3 (6)	7 (14)	
>38	44 (94)	43 (86)	

Characteristic	Ceftolozane/ Tazobactam (n = 47)	Standard of Care (n = 50)	*P* Value
Microbiological documentation (positivity)	13 (28)	12 (24)	.68
Site of microorganism(s)[a]			
Genitourinary tract	2	1	
Blood	11	12	
Gram-negative bacterial pathogen	4 (9)	2 (4)	.43
Gram-negative alone	2	2	
Gram-negative and -positive (mixed infection)	2	0	
Organisms recovered in positive cultures[b]			
Escherichia coli	0	2	
Klebsiella pneumoniae	1	0	
Pseudomonas aeruginosa	1	0	
MRSA	2	1	
Rothia mucilaginosa	1	0	
Streptococcus viridans	5	5	
Staphylococcus epidermidis	1	2	
Enterococcus faecalis	0	2	
E faecalis + E coli	1	0	
E faecalis + P aeruginosa	1	0	
CVC the source of BSI isolation	7/11 (64)	7/12 (58)	>.99
Hospital stay duration, d, median (IQR)	6 (4–9)	7 (4–11)	.84
ICU admission	2 (4)	3 (6)	>.99
Mechanical ventilation	2 (4)	1 (2)	.61

Chaftari AM, et al. Open Forum Infect Dis. 2022 Feb 14;9(6):ofac079.

Real World Evidence bei Neutropenie
Ceftolozan/Tazobactam

Table 2. Clinical Outcome of Patients Who Received Ceftolozane/Tazobactam and Those Who Received the Standard of Care

Clinical Outcome	Ceftolozane/Tazobactam (n = 47)	Standard of Care (n = 50)	*P* Value
Clinical outcome at EOIV			.10
Favorable clinical response	41 (87)	36 (72)	
Clinical failure	2 (4)	9 (18)	
ndeterminate	4 (9)	5 (10)	
Clinical outcome at TOC			.01
Clinical cure	34 (72)	28 (56)	
Clinical failure	3 (6)	15 (30)	
Indeterminate	10 (21)	7 (14)	
Clinical outcome at LFU			.028
Clinical cure	33 (70)	26 (52)	
Clinical failure	4 (9)	15 (30)	
Indeterminate	10 (21)	9 (18)	
Mortality during the study	3 (6)	2 (4)	.67
Duration between last dose of study drug and death, d, median (range)	17 (15–34)	29 (28–29)	.77
Infection-related mortality	0 (0)	0 (0)	
30-d all-cause mortality	2 (4)	2 (4)	>.99

Data are presented as No. of patients (%) unless otherwise specified.
Abbreviations: EOIV, end of intravenous therapy; LFU, late follow-up; TOC, test of cure.

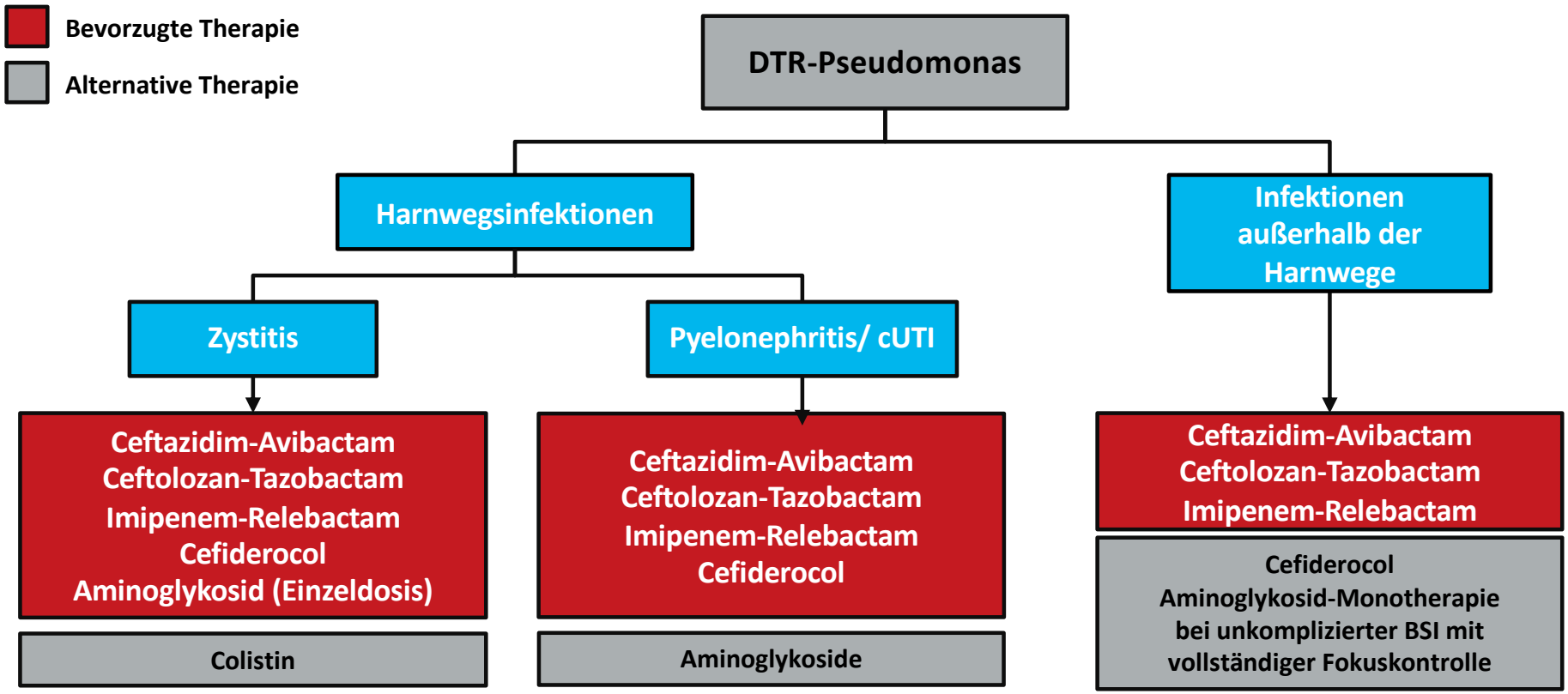
Table 3. Microbiological Outcome of Patients Who Received Ceftolozane/Tazobactam and Those Who Received the Standard of Care

Outcome	Ceftolozane/Tazobactam (n = 47)	Standard of Care (n = 50)	*P* Value
Microbiologically documented infection	13 (28)	12 (24)	.68
Microbiological response at EOIV			.86
Persistence	1/13 (8)	1/12 (8)	
Eradication	11/13 (85)	9/12 (75)	
Presumed eradication	0/13 (0)	1/12 (8)	
Indeterminate	1/13 (8)	1/12 (8)	
Microbiological response at TOC			.64
Persistence	0/13 (0)	1/12 (8)	
Eradication	3/13 (23)	2/12 (17)	
Presumed eradication	8/13 (62)	9/12 (75)	
Indeterminate	2/13 (15)	0/12 (0)	
Microbiological response at LFU			.33
Persistence	0/13 (0)	1/12 (8)	
Eradication	2/13 (15)	3/12 (25)	
Presumed eradication	81/3 (62)	8/12 (67)	
Indeterminate	3/13 (23)	0/12 (0)	
Relapse	0/12 (0)	0/11 (0)	

Data are presented as No. of patients (%) unless otherwise indicated.
Abbreviations: EOIV, end of intravenous therapy; LFU, late follow-up; TOC, test of cure.

Chaftari AM, et al. Open Forum Infect Dis. 2022 Feb 14;9(6):ofac079.

IDSA Guidance
Difficult-to-Treat (DTR) Pseudomonas



DTR – Difficult-to-treat-Resistance: NS to PIP-TAZ, CAZ, FEP, ATM, MER, IMI, CIP, LEV

Tamma PD, et al. Clin Infect Dis. 2022 Apr 19:ciac268.

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Ruhr-Universität Bochum


Schauspielhaus

Sepsis DataNet NRW

Glückauf !


Deutsches Bergbaumuseum

Backup Folien

Mono- oder Kombinationstherapie bei CRE

Individualisierte Entscheidung!

<u>Kombination erwägen bei:</u>

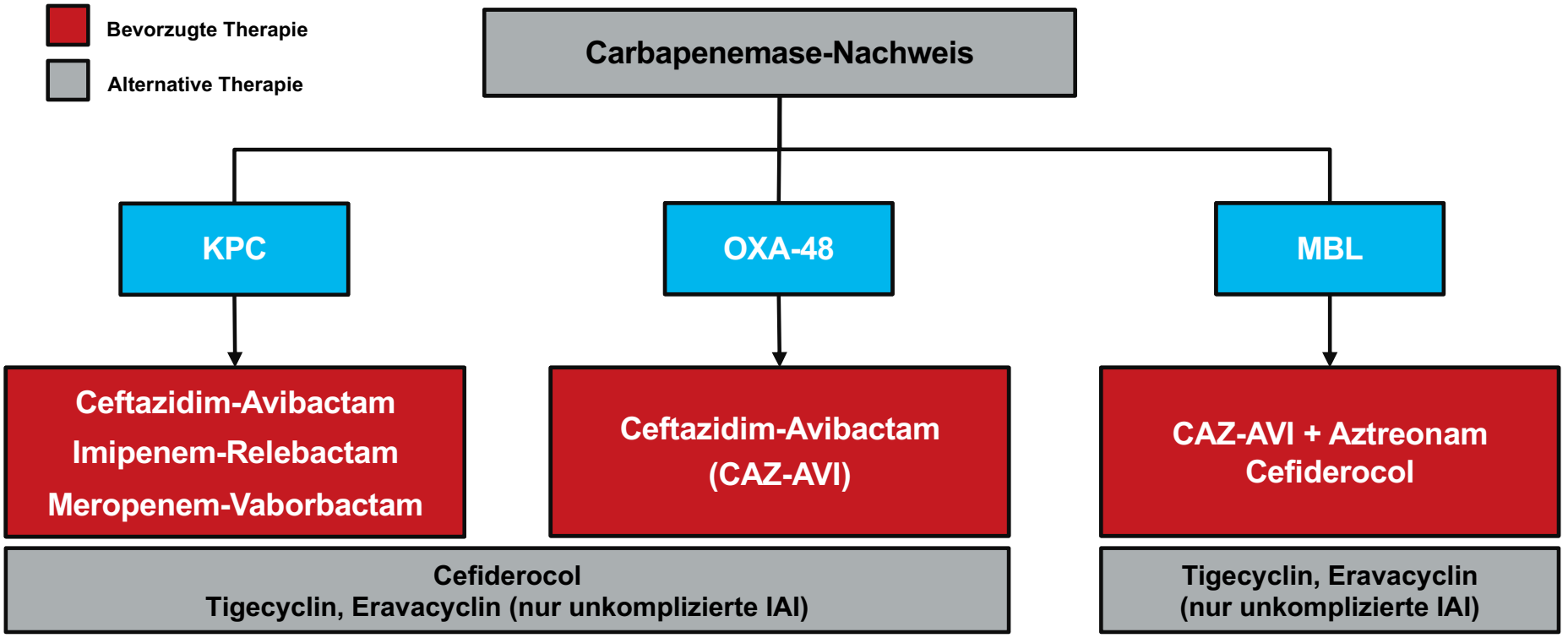
- Hoher Krankheitsschweregrad (?)
- Blutstrom > Pneumonie > Abdominell > Harnweg
- *<u>Kalkulierte Therapie</u>*
  - Hochrisiko für gram(-) multiresistenten Erreger
- *<u>Gezielte Therapie</u>*
  - *Regime **<u>ohne</u>** ß-Lactam Antibiotikum*
  - ß-Lactam-AB nicht "sicher" dosierbar

    → z.B. EUCAST 2019 „I" und kein TDM
    - ***<u>Ausnahme:</u>*** CR A. baumanii (CRAB)

      → Colistin-Monotherapie

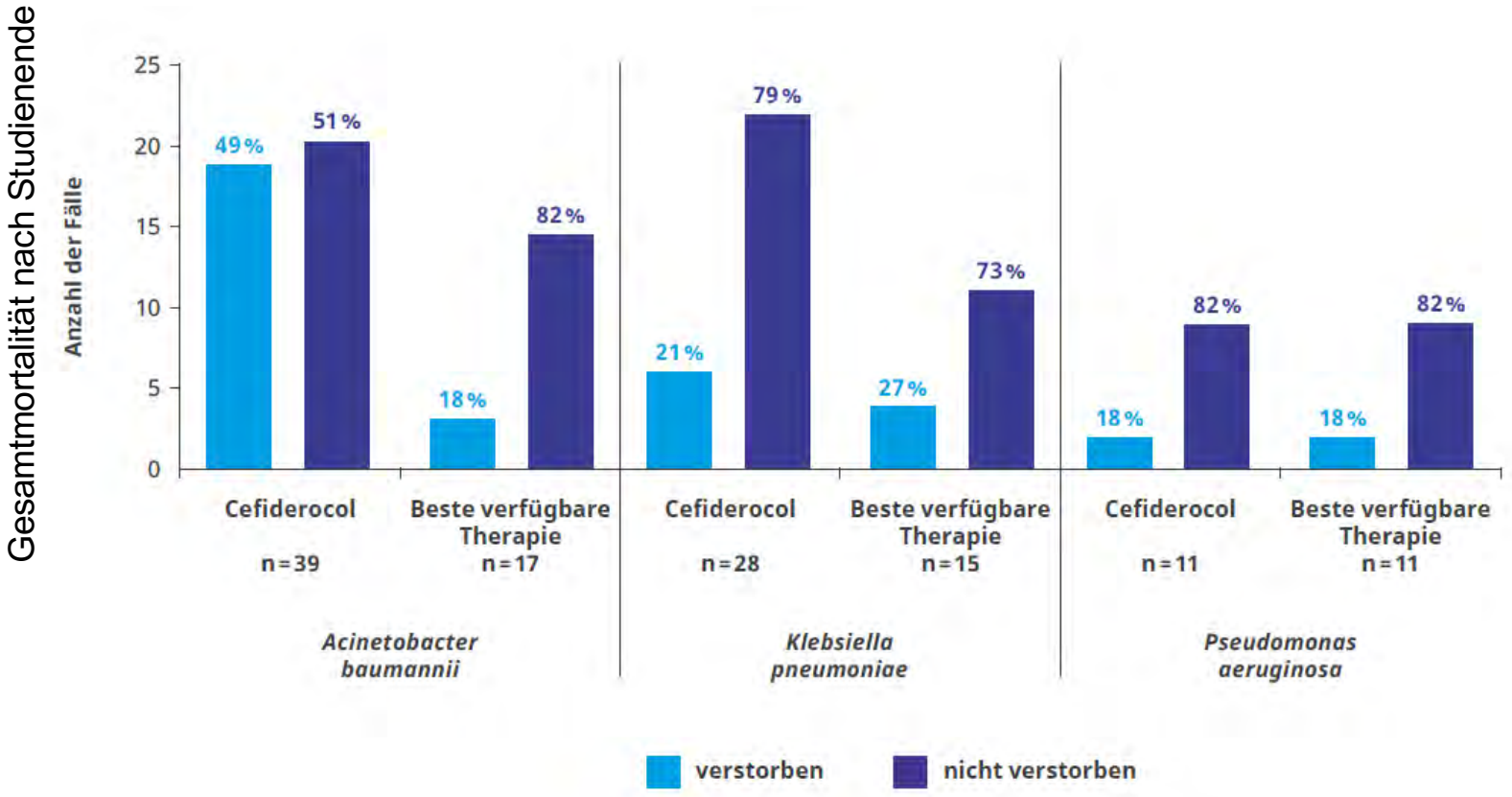
Karaiskos I, et al. Front Public Health. 2019 Jun 11;7:151.

IDSA Guidance
Carbapenem-resistente Enterobacterales



Tamma PD, et al. Clin Infect Dis. 2022 Apr 19:ciac268.

Ergebnisse CREDIBLE-CR Studie



Bassetti M, et al. Lancet Infect Dis. 2021 Feb;21(2):226-240.

Prioritäten-Liste der WHO
für die Entwicklung neuer Antibiotika

Priority 1: CRITICAL

- Acinetobacter baumannii, carbapenem-resistant
- Pseudomonas aeruginosa, carbapenem-resistant
- Enterobacteriaceae, carbapenem-resistant, ESBL-producing

Priority 2: HIGH

- Enterococcus faecium, vancomycin-resistant
- Staphylococcus aureus, methicillin-resistant, vancomycin-intermediate and resistant
- Helicobacter pylori, clarithromycin-resistant
- Campylobacter spp., fluoroquinolone-resistant
- Salmonellae, fluoroquinolone-resistant
- Neisseria gonorrhoeae, cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

- Streptococcus pneumoniae, penicillin-non-susceptible
- Haemophilus influenzae, ampicillin-resistant
- Shigella spp., fluoroquinolone-resistant

WHO 2017. https://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/