UNIVERSITÄTS KLINIKUM jena

Klinische Erfahrungen mit neuen Reserveantibiotika bei Gram-negativen Erregern

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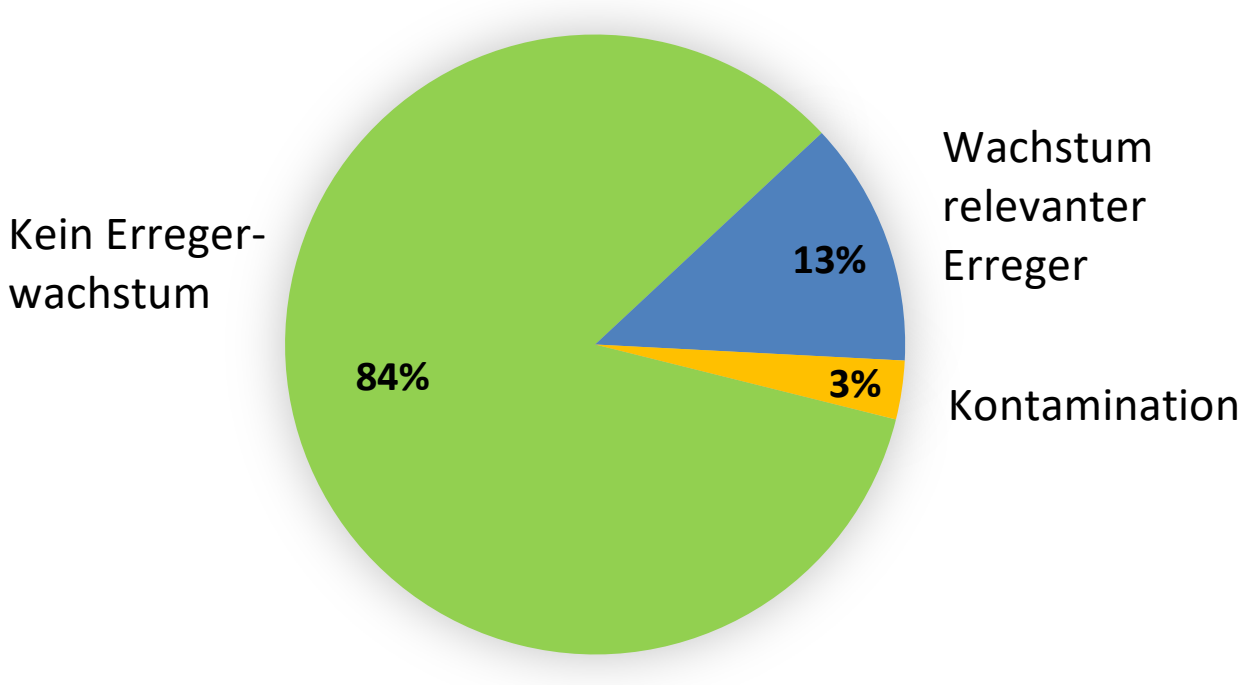
Interessenskonflikte

Vortragshonorare, Beratertätigkeit, Advisory Boards (5 Jahre)

- Pfizer
- MSD
- Shionogi
- InfectoPharm
- Advanzpharma
- Tillots Pharma
- Thermo Fisher
- Philips

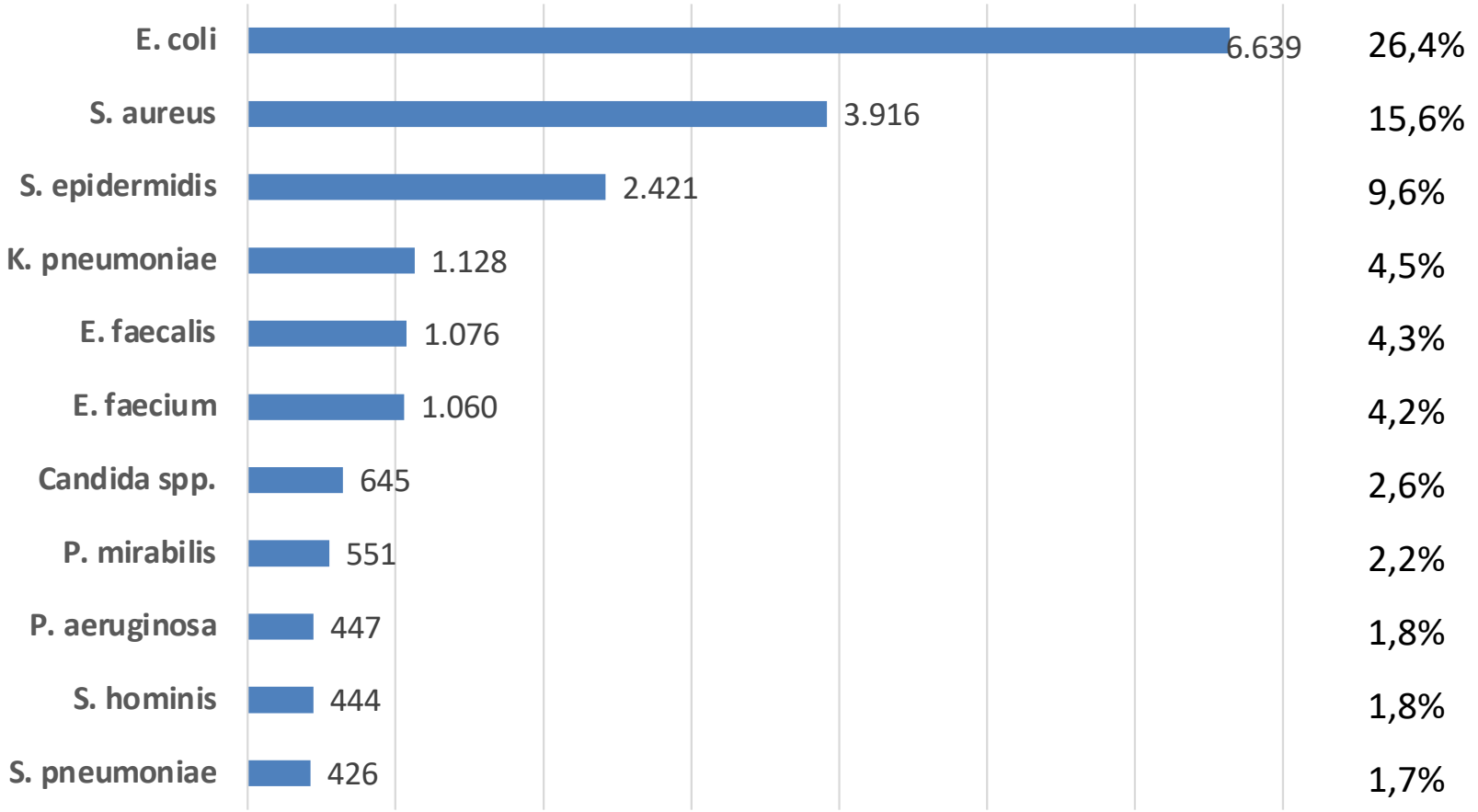
Epidemiologie - AlertsNet

- 26 Krankenhäuser Thüringen, 2015-2019
- 335.623 Blutkulturen (1x Aerob/1x Anaerob) bei 91.637 Pat.

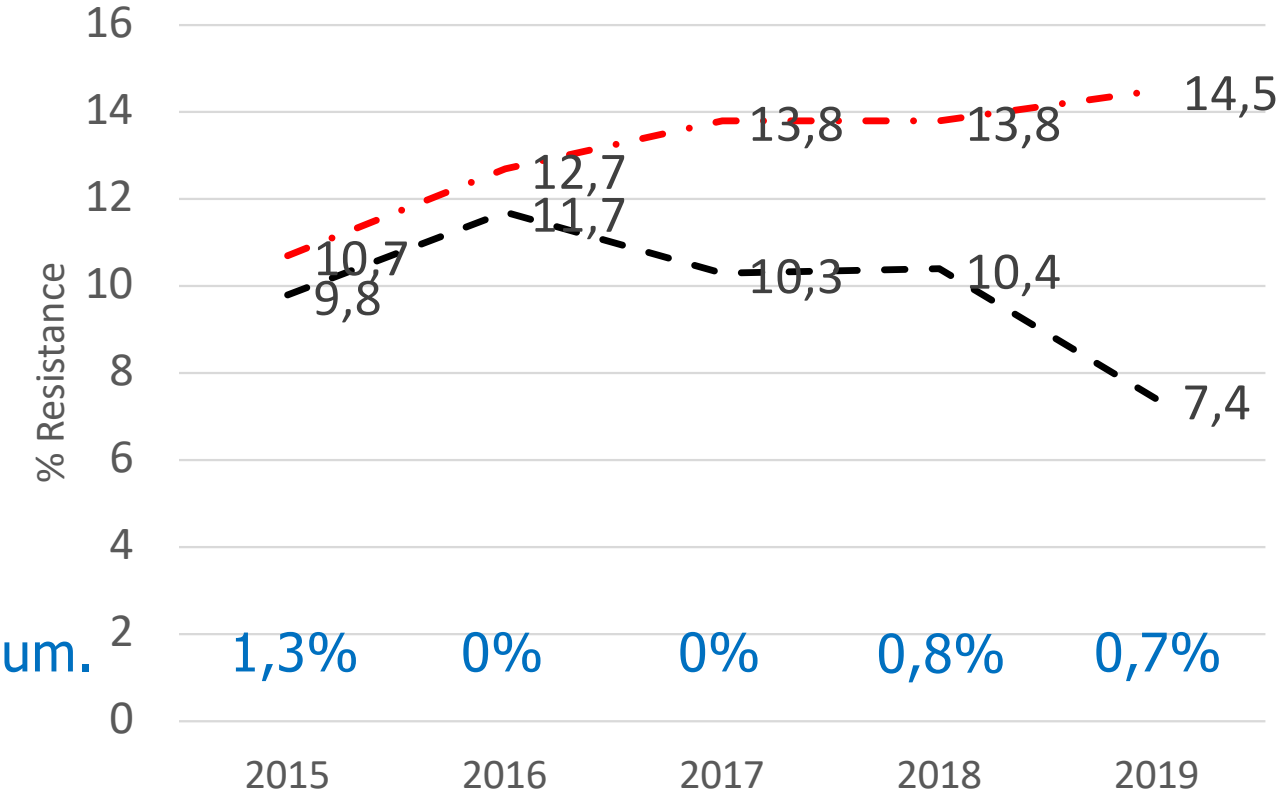


Schöneweck F. et al. Antimicrob Resist Infect Control (2021) 10:132

25.155 relevant positive Blutkulturen – Top 11



3G-Resistenz & CR-K. pneumoniae



3G- E.coli
(*ARS 2020: 10.4%)

3G- K. pneu
(*ARS 2020: 11.2%)

CR-K. pneum.	1,3%	0%	0%	0,8%	0,7%

Resistenzsituation in Deutschland 2016-2020 im europäischen Vergleich

Mikroorganismus x Antibiotikum/ Antibiotikaklasse	Deutschland						EARS-Net	
	2016	2017	2018	2019	2020	Trend	MW 2020	Trend
Escherichia coli								
Fluorchinolone R	19,4	20,7	19,8	17,5	16,5	–	23.8	–
Cephalosporine 3. Gen. R	11,1	12,3	12,2	11,5	10,3	–	14.9	–
Aminoglykoside R	7,0	7,0	6,9	8,3	7,5	+	10.9	+
Carbapeneme R	< 0,1	< 0,1	< 0,1	< 0,1	< 0,1		0.2	
kombinierte Resistenz **	3,4	3,7	3,4	3,1	2,7	–	5.7	–
Klebsiella pneumoniae								
Fluorchinolone R	12,6	15,3	13,4	13,1	11.6	–	33.8	–
Cephalosporine 3. Gen. R	13,6	14,6	12,9	12,2	11.0	–	33.9	–
Aminoglykoside R	7,7	8,2	6,2	7,3	5.6	–	23.7	–
Carbapeneme R	0,5	0,5	0,4	0,9	0.5		10.0	
kombinierte Resistenz **	5,3	6,3	4,7	4,8	3.7	–	21.0	–
Pseudomonas aeruginosa								
Piperacillin/TAZ R	15,0	12,6	12,4	11,7	11.7	–	18.8	–
Fluorchinolone R	12,4	13,9	12,4	13,4	10.6		19.6	–
Ceftazidim R	10,1	9,8	9,1	10,0	10.0		15.5	
Aminoglykoside R	6,8	4,8	3,5	4,1	2.0	–	9.4	–
Carbapeneme R	14,5	12,6	12,1	12,9	13.8		17.8	
kombinierte Resistenz **	7,3	6,6	5,8	6,3	6.6		12.1	
Acinetobacter spp.								
Aminoglykoside R	3,0	3,4	3,4	4,2	4.9		37.1	
Fluorchinolone R	5,7	6,5	6,8	5,0	5.1		41.8	
Carbapeneme R	4,9	4,1	4,4	2,2	3.5		38.0	
kombinierte Resistenz **	2,3	1,2	2,2	1,4	2.5		34.1	

Eckmanns und Abu Sin, Deutsches Ärzteblatt | Jg. 119 | Heft 12 | 25. März 2022

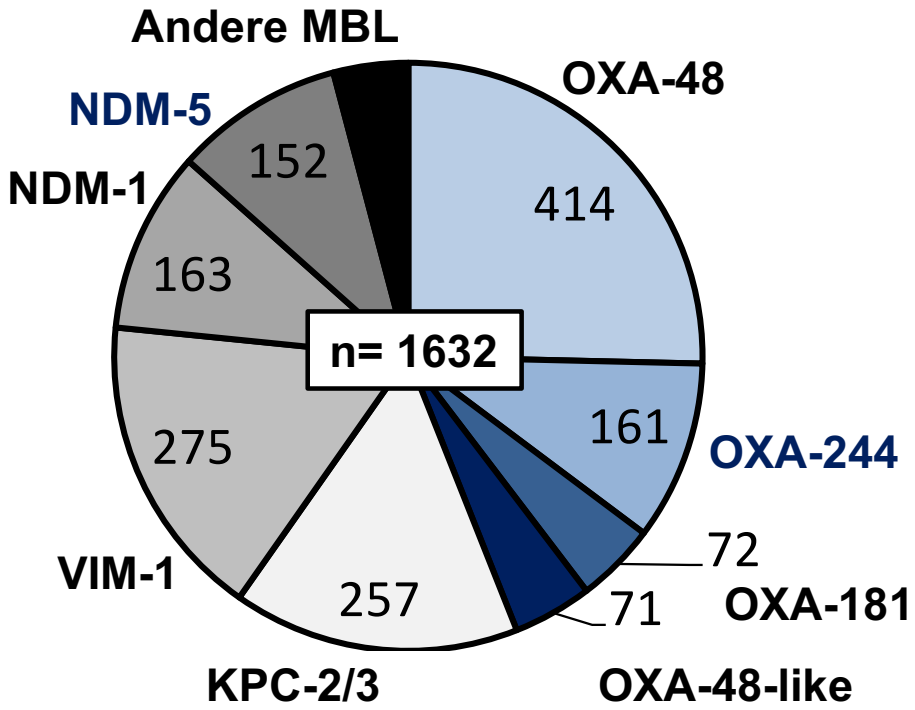
Anteil der Carbapenemase-produzierenden Isolate

	Anzahl der getesteten Isolate	Anteil der Carbapenemase-produzierenden Isolate
Enterobacterales	3.708	1.567 (42,3 %)
E. coli	726	460 (63,4 %)
K. pneumoniae	1.261	533 (42,3 %)
E. cloacae	629	244 (34,5 %)
K. aerogenes	422	13 (3,5 %)
andere Enterobacterales	670	317 (47,3 %)
P. aeruginosa	1.778	360 (20,2 %)
A. baumannii	346	334 (96,5 %)

Pfennigwerth N, Schauer J : Epid Bull 2021;36:4 -11

Carbapenemasen bei Enterobacterales in Deutschland

Nationales Referenzzentrum Bochum 2020



1. OXA-48
2. VIM-1
3. KPC-2/3
4. NDM-1

Pfennigwerth et al., P959, ECCMID 2021

“Neue” Therapieoptionen für MDR-GNB

P. aeruginosa Resistance Mechanism	Ceftolozane/ Tazobactam	Ceftazidime/ Avibactam	Meropenem/ Vaborbactam	Imipenem/ Relebactam	Eravacycline	Cefiderocol
Porin Reduction (eg, loss of OprD)	√	√	(√)	√		√
AmpC β-lactamase (ie, AmpC derepression)	√	√	√	√		√
Efflux Pumps (eg, MexAB, MexXY)	√			√		√
ESBLs / β-lactamases						
CTX-M, TEM, SHV	√	√	√	√	√	√
Carbapenemases						
KPCs / CPE		√	√	√	√	√
OXA-48 Producing Enterobacteriaceae	Ceftaz-S	√			+/-	√
Carbapenem-Resistant Acinetobacter					√	(√)
Metallo-β-lactamases					+/-	√

Bassetti M et al., Curr Opin Infect Dis, 2018

Agenda

- **Klinische Anwendung neuer Substanzen:**
    a. Ceftazidim/Avibactam
    b. Ceftazidim/Avibactam + Aztreonam
- **Zusammenfassung**

Ceftazidim/Avibactam

- **Seit Februar 2017 in Deutschland erhältlich (FDA 2015)**
- **Zulassung (Pädiatrische Patienten ab 3 Monate + Erwachsene)**
    a. komplizierte intraabdominelle Infektionen (mit Metronidazol)
    b. komplizierte Harnwegsinfektionen (inkl. Pyelonephritis)
    c. nosokomiale Pneumonie (inkl. VAP)
    d. Bakteriämie im Zusammenhang oder Verdacht auf „a-c"*
    e. Infektionen aufgrund Gram-negativer Erreger bei Patienten mit begrenzten Behandlungsoptionen

* bei erwachsenen Patienten

Ceftazidim/Avibactam Zulassungsstudien

- **RECLAIM I + II**
  - cIAI, n=1.066
  - Nichtunterlegenheit gegenüber Meropenem
- **RECAPTURE I + II**
  - cUTI, n=1.033
  - Nichtunterlegenheit gegenüber Doripenem
- **REPRISE**
  - cUTI+cIAI, n=333
  - Ceftazidim resistente Erreger
  - Best available therapy (97% Carbapenem)
- **REPROVE**
  - HAP/HAP, n=879
  - Nichtunterlegenheit gegenüber Meropenem

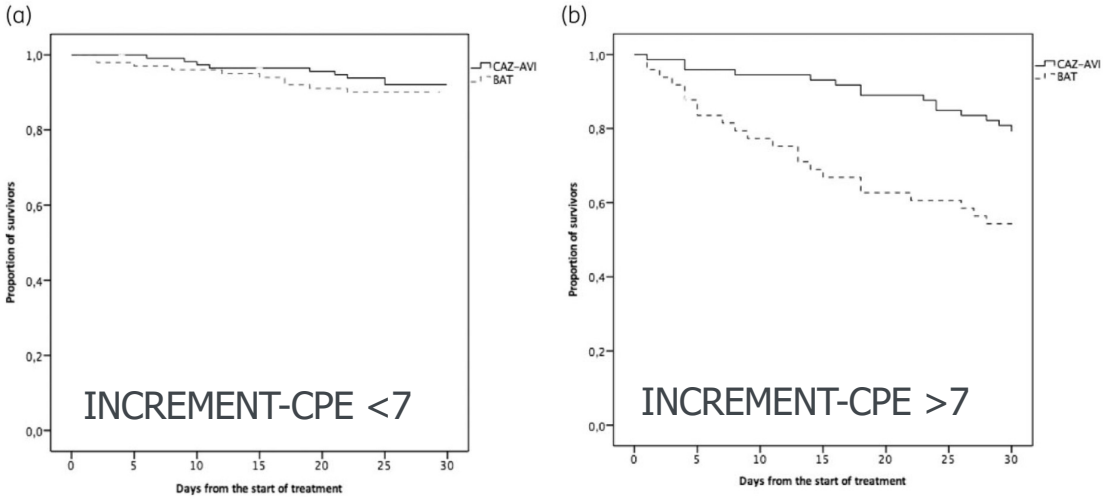
Impact of ceftazidime/avibactam versus best available therapy on mortality from infections caused by carbapenemase-producing Enterobacterales (CAVICOR study)

- 14 Kliniken, Spanien, retrospektive Beobachtungsstudie
- Juni 2014 – Dezember 2019
- Mindestens 48h Therapie
- 339 Pat. (CAZ-AVI: n=189 oder BAT: n=150)
- 163 K. pneumoniae, 8 E. cloacae, 3 E. coli (109 OXA-48, 62 KPC, 1 OXA-48 plus KPC)
- Therapiebeginn: Median 2 Tage (IQR 1-4) nach Diagnosestellung
- Fokus: 38% cUTI, 33% Blutstrominfektion

Castón et al., J Antimicrob Chemother, Januar 2022

Impact of ceftazidime/avibactam versus best available therapy on mortality from infections caused by carbapenemase-producing Enterobacterales (CAVICOR study)

- Overall 30-Tage Sterblichkeit: 17.4% (Pneumonie 28% → 10% IAI)
- CAZ-AVI: 13.7% vs. 22% BAT, p=0.04



21.9% vs. 46.9%, sig.

Severe sepsis or septic shock	5 pts
Pitt score ≥6	4 pts
Charlson comorbidity index ≥2	3 pts
Source of BSI other than urinary or biliary tract	3 pts

Castón et al., J Antimicrob Chemother, Januar 2022

Impact of ceftazidime/avibactam versus best available therapy on mortality from infections caused by carbapenemase-producing Enterobacterales (CAVICOR study)

- Kombinationstherapie zeigte keinen Benefit
  - CAZ-AVI (single vs combi): 14.3% vs. 12.5%, p=0.82
- Multivariat Analyse (unabhängiger Faktor)
  - 30d-Sterblichkeit: CAZ-AVI OR 0.41, 95% CI 0.20–0.80; p=0.01
  - Klinische Heilung: CAZ-AVI OR 2.43, 95% CI 1.16–5.12; p=0.02
  - Mikrobio. Versagen: CAZ-AVI OR 0.40; 95% CI 0.18–0.85; p=0.02
- Nebenwirkungen CAZ-AVI 5.8% vs. 20% BAT, p<0.001

Castón et al., J Antimicrob Chemother, Januar 2022

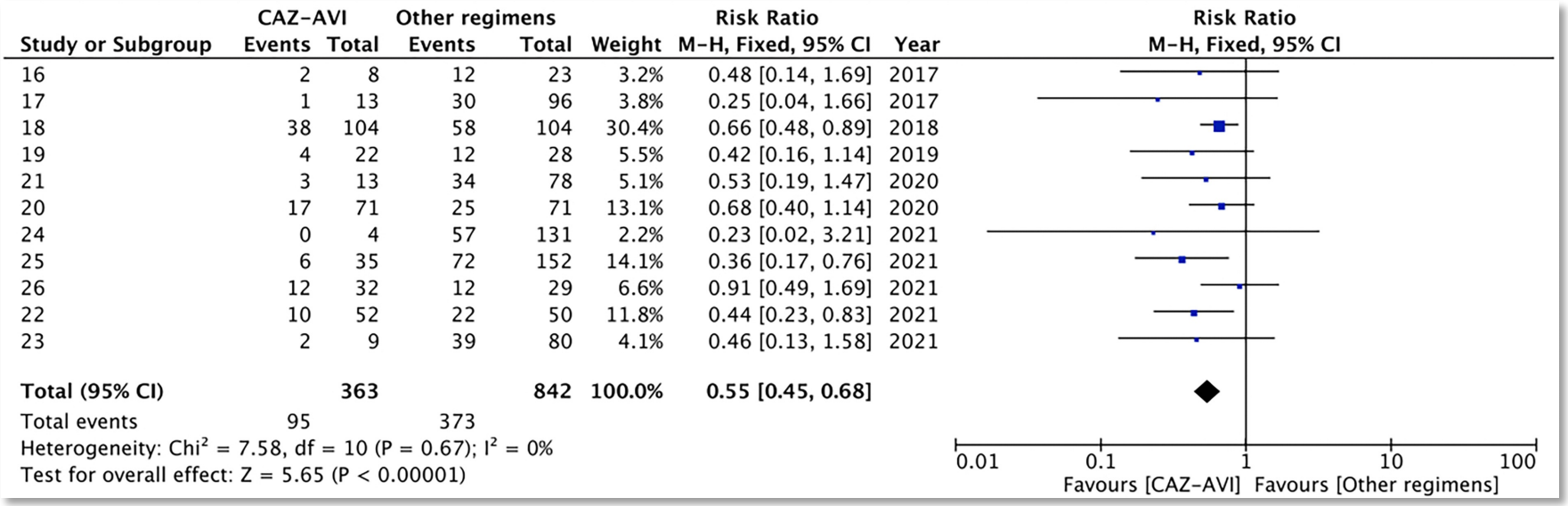
Efficacy and Safety of Ceftazidime-Avibactam for the Treatment of Carbapenem-Resistant *Enterobacterales* Bloodstream Infection: a Systematic Review and Meta-Analysis

Yan Chen,[a] Hui-Bin Huang,[b] Jin-Min Peng,[a] Li Weng,[a] Bin Du[a]

- Literatur bis November 2021
- 11 Studien (3 prospektiv, 8 retrospektiv), 1205 Patienten
  - → V.a. KPC als Resistenzmechanismus
  - → In Vergleichsgruppe am häufigsten Colistin+Tigecyclin Kombinationstherapie
  - → Bei CAZ-AVI häufig zusätzlich Meropenem oder Tigecyclin als Kombinationspartner

Microbiology Spectrum, March/April 2022 Volume 10, Issue 2

30-Tage Sterblichkeit



Study or Subgroup	CAZ-AVI Events	CAZ-AVI Total	Other regimens Events	Other regimens Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
16	2	8	12	23	3.2%	0.48 [0.14, 1.69]	2017
17	1	13	30	96	3.8%	0.25 [0.04, 1.66]	2017
18	38	104	58	104	30.4%	0.66 [0.48, 0.89]	2018
19	4	22	12	28	5.5%	0.42 [0.16, 1.14]	2019
21	3	13	34	78	5.1%	0.53 [0.19, 1.47]	2020
20	17	71	25	71	13.1%	0.68 [0.40, 1.14]	2020
24	0	4	57	131	2.2%	0.23 [0.02, 3.21]	2021
25	6	35	72	152	14.1%	0.36 [0.17, 0.76]	2021
26	12	32	12	29	6.6%	0.91 [0.49, 1.69]	2021
22	10	52	22	50	11.8%	0.44 [0.23, 0.83]	2021
23	2	9	39	80	4.1%	0.46 [0.13, 1.58]	2021
Total (95% CI)		**363**		**842**	**100.0%**	**0.55 [0.45, 0.68]**	
Total events	95		373				

Heterogeneity: $Chi^2 = 7.58$, df = 10 (P = 0.67); $I^2 = 0\%$

Test for overall effect: Z = 5.65 (P < 0.00001)

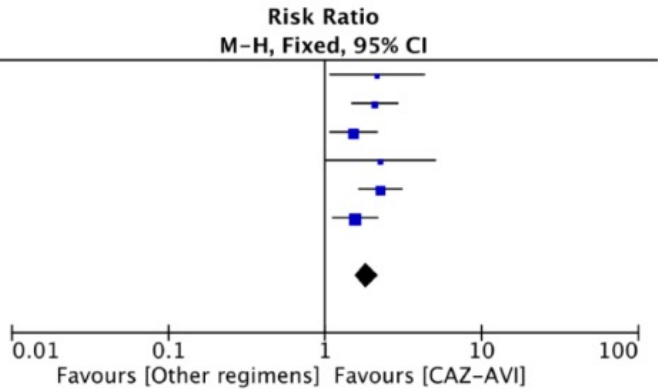
30-Tage Sterblichkeit: RR = 0.55, 95% CI 0.45 - 0.68, I^2 = 0%, p=0.00001

Vergleichsgruppe Colisitin: RR = 0.48, 95% CI 0.33 - 0.69, I^2 = 36%, p=0.0001

Klinische Heilung und Nephrotoxizität

Study or Subgroup	CAZ-AVI Events	CAZ-AVI Total	Other regimens Events	Other regimens Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Caston 2017	6	8	8	23	5.0%	2.16 [1.08, 4.29]	2017
Shields 2017	11	13	39	96	11.3%	2.08 [1.49, 2.91]	2017
Tsolaki 2019	33	41	19	36	24.6%	1.53 [1.08, 2.15]	2019
Hakeam 2021	15	32	6	29	7.6%	2.27 [1.02, 5.05]	2021
Chen 2021	25	35	48	152	21.8%	2.26 [1.65, 3.10]	2021
Falcone 2021	39	52	24	50	29.7%	1.56 [1.13, 2.17]	2021
Total (95% CI) (=567)		**181**		**386**	**100.0%**	**1.85 [1.57, 2.18]**	
Total events	129		144				

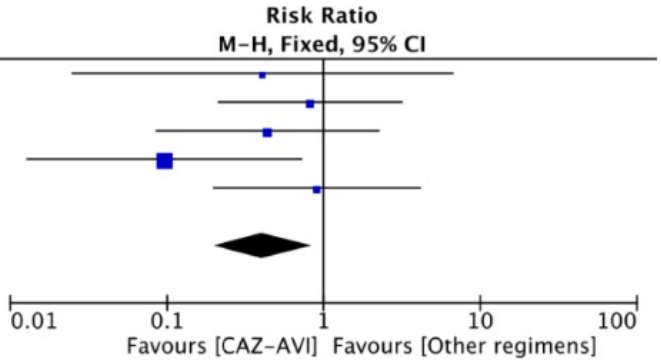
Heterogeneity: $Chi^2 = 4.72$, df = 5 (P = 0.45); $I^2 = 0\%$
Test for overall effect: Z = 7.29 (P < 0.00001)



Klinische Heilung

Study or Subgroup	CAZ-AVI Events	CAZ-AVI Total	Other regimens Events	Other regimens Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Shields 2017	0	13	8	96	9.2%	0.41 [0.02, 6.68]	2017
Caston 2017	2	8	7	23	15.5%	0.82 [0.21, 3.17]	2017
Tsolaki 2019	2	41	4	36	18.2%	0.44 [0.09, 2.26]	2019
Falcone 2021	1	52	10	50	43.6%	0.10 [0.01, 0.72]	2021
Hakeam 2021	3	32	3	29	13.5%	0.91 [0.20, 4.14]	2021
Total (95% CI) (=455)		**146**		**234**	**100.0%**	**0.41 [0.20, 0.84]**	
Total events	8		32				

Heterogeneity: $Chi^2 = 4.06$, df = 4 (P = 0.40); $I^2 = 2\%$
Test for overall effect: Z = 2.42 (P = 0.02)



Nephro-toxizität

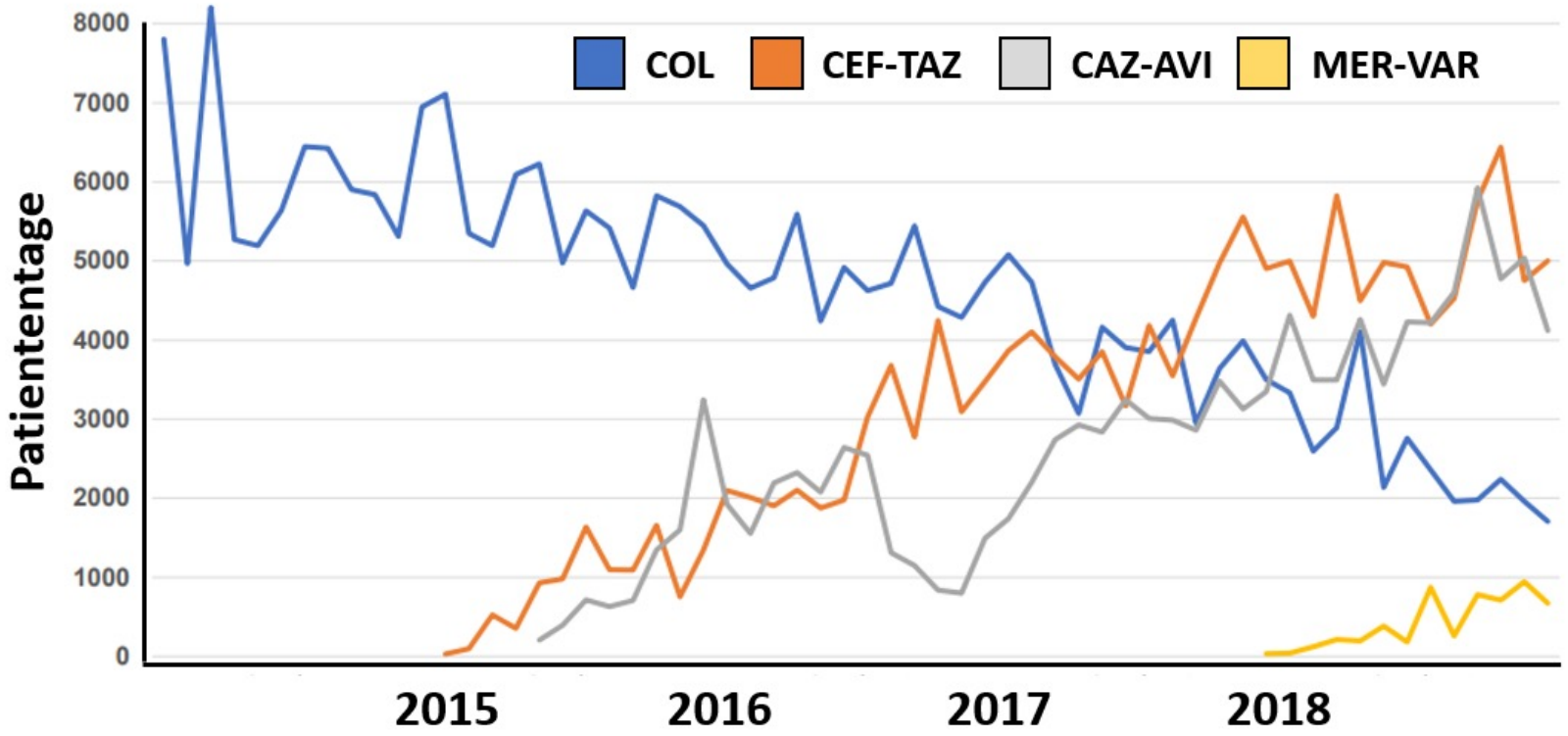
IDSA – CRE Empfehlungen 2020

Question 6: What is the role of polymyxins for the treatment of infections caused by CRE?

Recommendation: Polymyxin B and colistin should be avoided for the treatment of infections caused by CRE. Colistin can be considered as a last resort for uncomplicated CRE cystitis.

BL/BLIs haben Colistin verdrängt

US Premier Healthcare Database 2014-2019



Marcella et al., P833, ID Week 2020

› Clin Infect Dis. 2022 May 6;ciac354. doi: 10.1093/cid/ciac354. Online ahead of print.

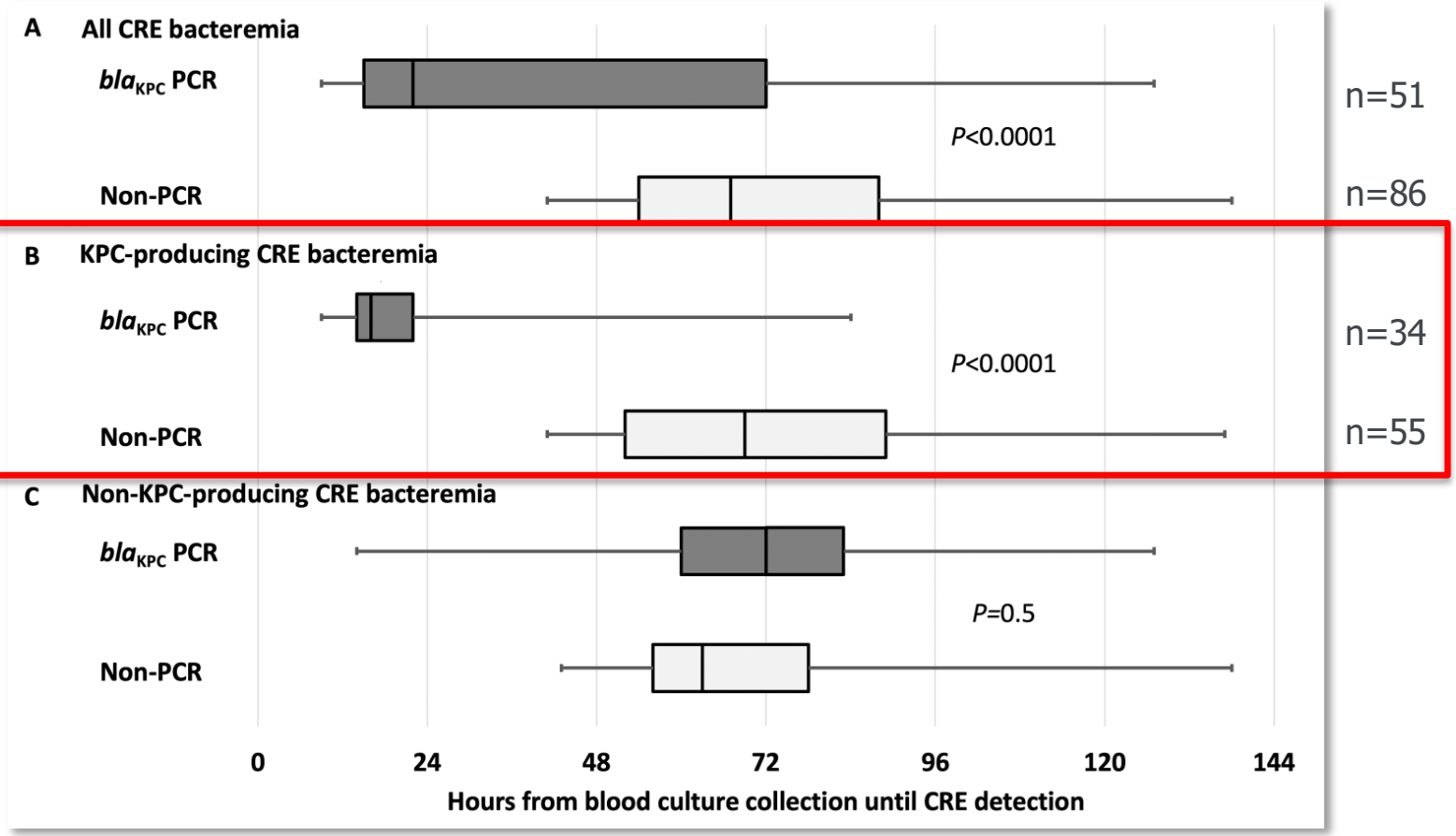
Impact of a Rapid Molecular Test for Klebsiella pneumoniae Carbapenemase and Ceftazidime-Avibactam Use on Outcomes after Bacteremia Caused by Carbapenem-Resistant Enterobacterales

Schnell sein!

- Beobachtungsstudie, 8 Kliniken New York & New Jersey, 2016-2018
- In 3 Kliniken *bla*$_{KPC}$PCR (BCID, BioFire) etabliert
- 137 Pat mit CRE-BSI (davon 89 Pat. KPC+)
  - → 51 Pat. haben *bla*$_{KPC}$PCR bekommen
  - → 32 Pat KPC positiv getestet (1x falsch neg)

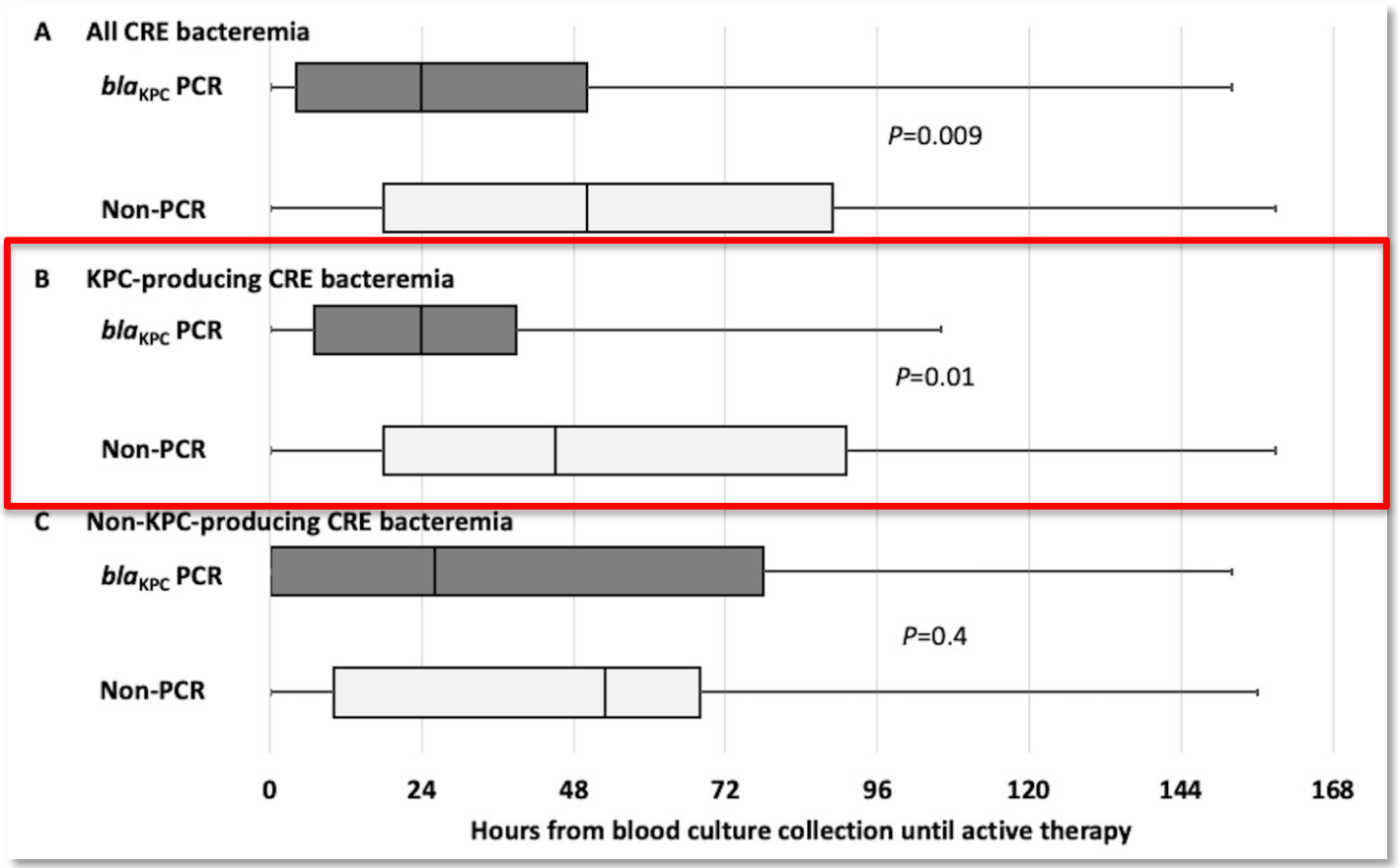
Satlin et al., CID, 2022, Mai 6, online

Schnellere Befundmitteilung: 16h vs. 64h



Satlin et al., CID, 2022, Mai 6, online

Schnellere adäquate Therapie.....



< 24h:

43% vs. 24%, p=0.02

<48 h:

63% vs. 37%, p=0.02

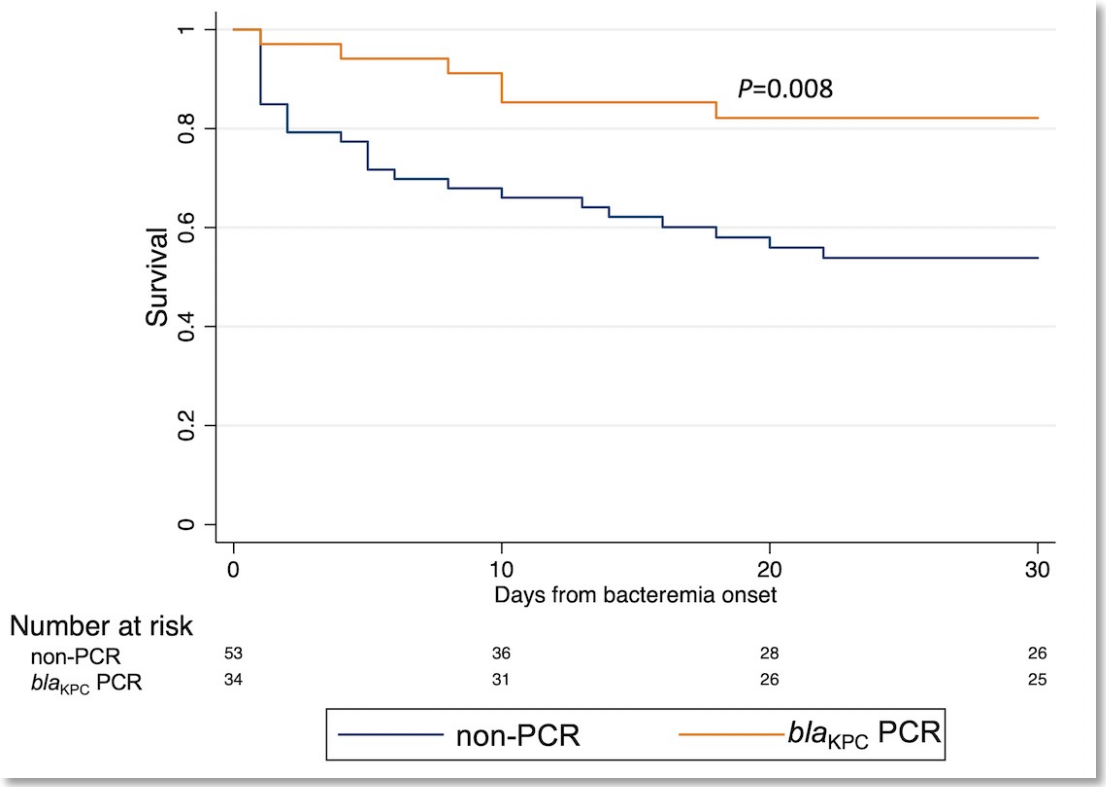
Satlin et al., CID, 2022, Mai 6, online

geringere Sterblichkeit.....

Sterblichkeit (PCR vs. non-PCR):

14 Tage: 16% vs. 37%, p=0.007

30 Tage: 24% vs. 47%, p=0.007

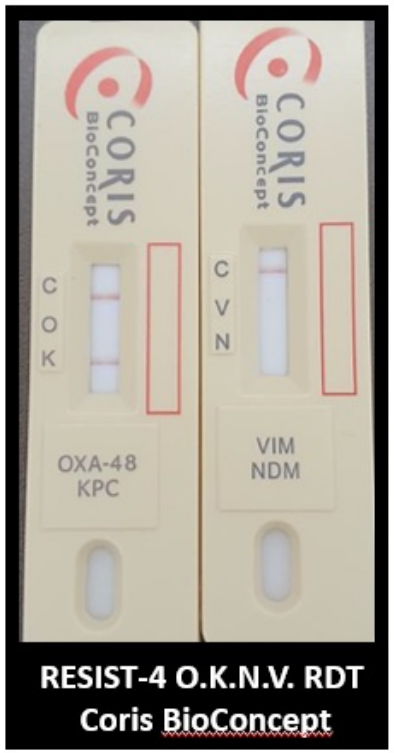


Pat mit KPC-BSI: OR 0.35, (0.16-0.75)

Satlin et al., CID, 2022, Mai 6, online

Reduktion der Zeit bis zur adäquaten Therapie

Immunchromatographischer Carbapenemase-Schnelltest



- 38 Patienten mit Verdacht auf Carbapenem-Resistenz
- Carbapenemase-Schnelltest aus positiven Blutkulturen (Pellets, innerhalb 2h) und klinischem Untersuchungsmaterial mit Wachstum von gram-neg Bakterien (Liquor, Drainagematerial, Urin, BAL etc.)
- 12 Patienten → Detektion KPC oder OXA-48 → Switch auf Ceftazidim-Avibactam
- Vergleich mit PCR → 100% Übereinstimmung

Roth et al., Eur J Clin Microbiol Infect Dis, Epub 7.9.2020

Molecular AST	
CTX-M	Not detected
KPC	DETECTED
OXA-48	Not detected
IMP	Not detected
VIM	Not detected
NDM	Not detected

Antibiotic	MIC mg/L (S/I/R)
Amoxi/Clav	>64 R
Pip/Tazo	>128 R
Ceftriaxone	>4 R
Ceftazidime	>128 R
Cefepime	>32 R
Meropenem	>64 R
Fosfomycin	32 S
Amikacina	>16 R
Gentamicin	1 (S)
Ciprofloxacin	>4 R
Colistin	1 (S)
CAZ/AVI	4 S
MER/VBR	1 S

KPC-3

Molecular AST	
CTX-M	Not detected
KPC	DETECTED
OXA-48	Not detected
IMP	Not detected
VIM	Not detected
NDM	Not detected

Antibiotic	MIC mg/L (S/I/R)
Amoxi/Clav	>64 R
Pip/Tazo	32 R
Ceftriaxone	>4 R
Ceftazidime	>128 R
Cefepime	16 R
Meropenem	2 S
Fosfomycin	>128 R
Amikacina	>16 R
Gentamicin	1 (S)
Ciprofloxacin	>4 R
Colistin	0.5 (S)
CAZ/AVI	32 R
MER/VBR	0.5 S

KPC-31

Molecular AST	
CTX-M	Not detected
KPC	DETECTED
OXA-48	Not detected
IMP	Not detected
VIM	Not detected
NDM	Not detected

Antibiotic	MIC mg/L (S/I/R)
Amoxi/Clav	>64 R
Pip/Tazo	>128 R
Ceftriaxone	>4 R
Ceftazidime	>128 R
Cefepime	>32 R
Meropenem	>64 R
Fosfomycin	32 S
Amikacin	8 (S)
Gentamicin	>8 R
Ciprofloxacin	>4 R
Colistin	>8 R
CAZ/AVI	16 R
MER/VBR	32 R

KPC-3 overexpressed

ECCMID 2022, Rossolini, Rapid diagnostic testing: is it a life saver for immunocompromised patients?, Antonelli et al. JAC, 2019 Aug 1, 74(8)

Ceftazidime-Avibactam Therapy Versus Ceftazidime-Avibactam-Based Combination Therapy in Patients With Carbapenem-Resistant Gram-Negative Pathogens: A Meta-Analysis

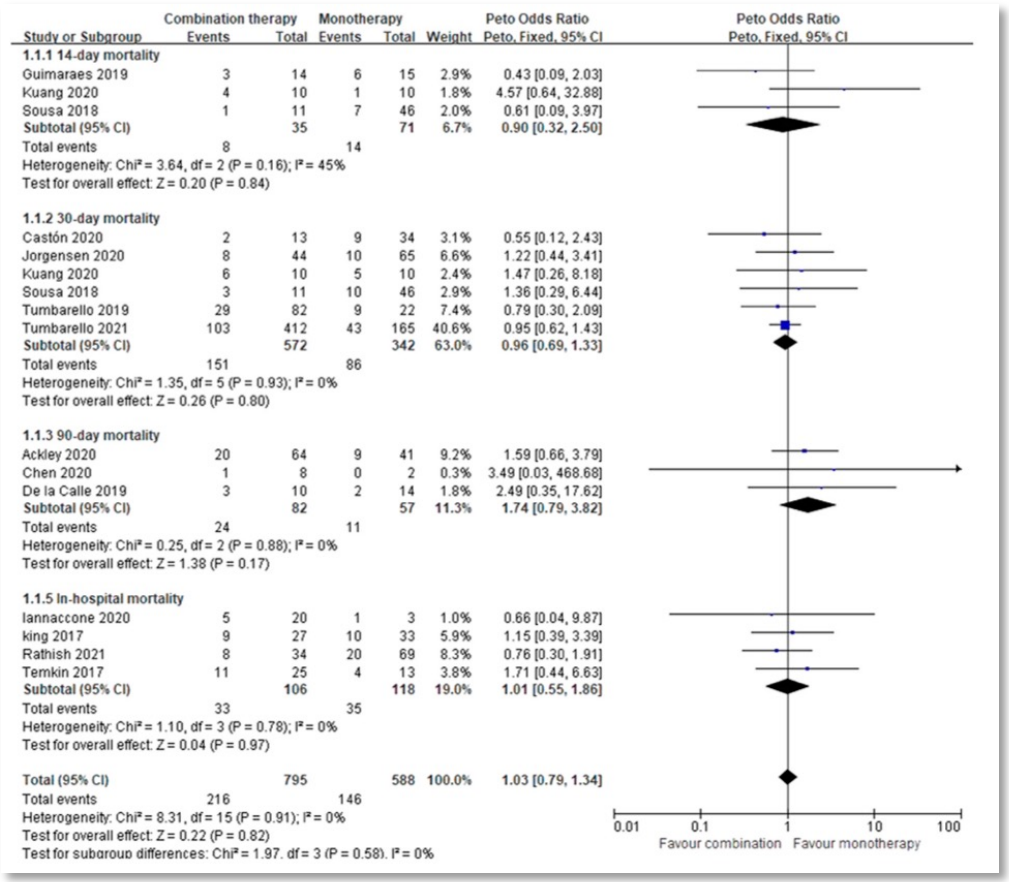
Dan Li[1,2,3†], Fan Fei[4†], Hua Yu[2], Xiangning Huang[2], Shanshan Long[2], Hao Zhou[5] and Jie Zhang[2*]*

Kombinationstherapie?

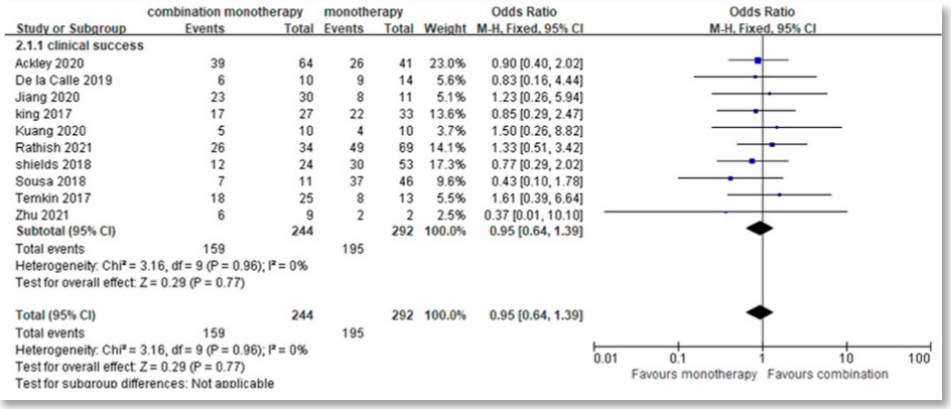
- Literatur bis März 2021
- 17 Studien, 1435 Patienten (873 Kombinations- / 598 Monotherapie CAZ-AVI)
- Am häufigsten Carbapenem-resistente Enterobacteriaceae, v.a. Klebsiella pneumoniae

Li et al., Frontiers in Pharmacology, Sept 2021, Volume 12

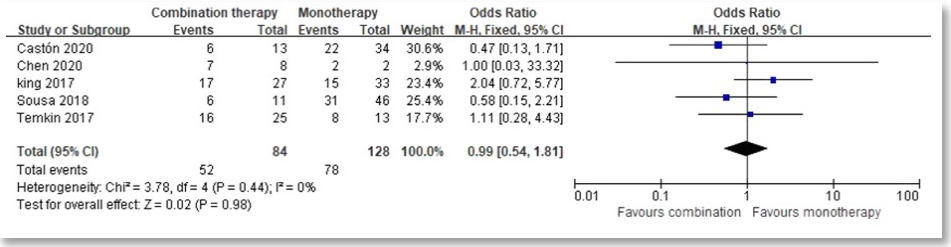
Kein Unterschied bei der Sterblichkeit



Klinische Heilung



Mikrobiologische Heilung



Li et al., Frontiers in Pharmacology, Sept 2021, Volume 12

“Neue” Therapieoptionen für MDR-GNB

	Ceftolozane/ Tazobactam	Ceftazidime/ Avibactam	Meropenem/ Vaborbactam	Imipenem/ Relebactam	Eravacycline	Cefiderocol
***P. aeruginosa* Resistance Mechanism**						
Porin Reduction (eg, loss of OprD)	√	√	(√)	√		√
AmpC β-lactamase (ie, AmpC derepression)	√	√	√	√		√
Efflux Pumps (eg, MexAB, MexXY)	√			√		√
ESBLs / β-lactamases						
CTX-M, TEM, SHV	√	√	√	√	√	√
Carbapenemases						
KPCs / CPE		√	√	√	√	√
OXA-48 Producing Enterobacteriaceae	Ceftaz-S	√			+/-	√
Carbapenem-Resistant Acinetobacter					√	(√)
Metallo-β-lactamases					+/-	√

Bassetti M et al., Curr Opin Infect Dis, 2018

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Efficacy of Ceftazidime-avibactam Plus Aztreonam in Patients With Bloodstream Infections Caused by Metallo-β-lactamase–Producing Enterobacterales

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- Retrospektive Beobachtungsstudie, Greece, Italy
- 102 Pt.: 82 NDM (79 K. pneum, 3 E. coli); 20 VIM (14 K. pneum., 5 Enterobacter, 1 Morganella)
- Fokus: 32% Harnwege, 26.5% Gefäßkatheter
- 52 Pt. Caz/Avi (2.5g 8h) + Aztreonam (2g 8h) vs. 50 Pt. andere aktive Substanzen (Tigecyclin/Colistin/Fosfomycin)

Ceftazidim-Avibactam PLUS Aztreonam in MBL-Enterobakterien

30-Tage Sterblichkeit:

- CAZ/AVI+ATM vs. Andere:

  19.2% vs. 44% (p=0.007)

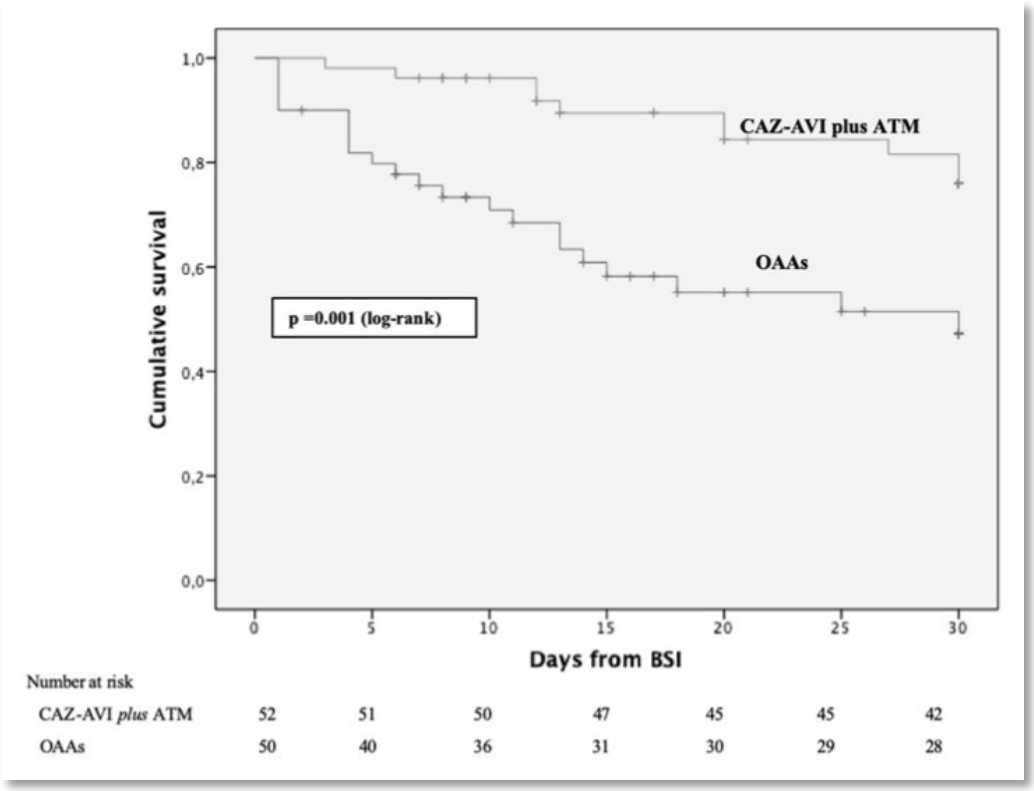
- CAZ/AVI+ATM vs. Colistin basiert:

  26.1% vs. 59.3% (p=0.019)

Therapieversagen an Tag 14:

CAZ/AVI+ATM HR 0.30

(95% CI, 0.14 –.65; p=0.002)



Falcone et al., Clin Infect Dis, 2021:72 (1 Juni)

Ceftazidim-Avibactam PLUS Aztreonam in MBL-Enterobakterien

Cox Regressions Analyse – Fkt. unabhängig mit 30d Sterblichkeit assoziiert

Factor	HR (95% CI)	*P* Value
Cardiovascular disease	6.62 (2.77–15.78)	< .001
Solid organ transplantation	3.52 (1.42–8.69)	.006
SOFA score (1-point increment)	1.21 (1.1–1.32)	< .001
CAZ-AVI + ATM (vs OAAs)	0.17 (.07–.41)	< .001

Abbreviations: ATM, aztreonam; CAZ-AVI, ceftazidime-avibactam; CI, confidence interval; HR, hazard ratio; OAAs, other active antibiotics; SOFA, Sequential Organ Failure Assessment.

Falcone et al., Clin Infect Dis, 2021:72 (1 Juni)

ID Society America Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections: **CRE Enterobacterales**

Table 3. Recommended antibiotic treatment options for carbapenem-resistant Enterobacterales (CRE), assuming *in vitro* susceptibility to agents in table

Source of Infection	**Preferred Treatment**	**Alternative Treatment** (first-line options not available or tolerated)
KPC identified (Or carbapenemase positive but identity of carbapenemase unknown[3])	Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam	Cefiderocol Tigecycline, eravacycline (intra-abdominal infections)
Metallo-β-lactamase (i.e., NDM, VIM, or IMP) carbapenemase identified	Ceftazidime-avibactam + aztreonam, cefiderocol	Tigecycline, eravacycline (intra-abdominal infections)
OXA-48-like carbapenemase identified	Ceftazidime-avibactam	Cefiderocol Tigecycline, eravacycline (intra-abdominal infections)

Zusammenfassung

1. Weiterhin vergleichsweise niedrige Inzidenz von Carbapenem-resistenten Gram-negativen Bakterien in Deutschland.
2. Schnelle Diagnostik und adäquate Therapie geht mit einem besseren Outcome einher.
4. Zunehmend klinische Daten über den Stellenwert von Ceftazidim/Avibactam bei der Therapie von v.a. OXA-48 und KPC Infektionen

   → Outcome besser als BAT, Nephrotoxizität geringer als unter Colisitin

   → Monotherapie mit CAZ-AVI scheint adäquat
5. Bei NDM, VIM → CAZ-AVI in Kombination mit Aztreonam als Option