Medizinische Universität Graz

Neue Therapieoptionen bei Non-fermenter Infektionen

Update zu Real-World Erfahrung mit BL/BLI-Kombinationen

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Nonfermenter

- Acinetobacter
- Pseudomonas
- Burkholderia
- Stenotrophomonas

BL/BLI Kombinationen

- Ampicillin/Sulbactam
- Amoxicillin/Clavulansäure
- Piperacillin/Tazobactam

- **Ceftolozan/Tazobactam**
- **Ceftazidim/Avibactam**

BLI-Turnover

- Staph aureus Penicillinase: Clavulansäure 1
- TEM: Clavulansäure 160, Sulbactam 10000, Tazobactam 140
- SHV: Clavulansäure 60, Sulbactam 13000, Tazobactam 5

Drawz. CMR 2010,23:160–201

In Vitro Aktivität von Ceftolozan gegenüber *Pseudomonas aeruginosa* Isolaten von Patienten mit Zystischer Fibrose

- 100 *P. aeruginosa* Isolate von 50 Patienten mit Zystischer Fibrose (Spanien)
- $MIC_{50/90}$ für Ceftolozan war 0.5/2 mg/L
- Ceftolozan war das einzige der getesteten Antibiotika, bei dem sich die Suszeptibilität (%S) nicht verringerte (early/late: Zeitintervall zwischen der ersten und letzten verfügbaren Probe lag zwischen 2 und 163 Monaten, Durchschnitt: 67,6 Monate)

Antibiotikum	Suszeptibilität (S)				%S (early/late)
	MHK_{50} (early)	MHK_{50} (late)	MHK_{90} (early)	MHK_{90} (late)	
Ceftolozan	0.5	1	2	4	95/96
Ceftazidim	4	8	64	128	75/70
Cefepim	8	8	32	64	63/60
Piperacillin/Tazobactam	4	4	128	128	87/84
Meropenem	0.5	0.5	8	16	86/82

Zamorano et al. *Clin Microbiol Infect.* 2010;16:1482-7.

Pseudomonas aeruginosa Resistenzmechanismen Aktivität von Ceftolozan

	äußere Membran: Verlust des Porins	β-Lactamase-enzyme	Efflux Pumpe	Efflux Pumpe
	OprD	**AmpC**	**MexXY**	**MexAB**
Ceftolozan[1]	0	+	0	0
Ceftazidim[2]	0	++++	0	++
Imipenem[3-6]	++++	0/+	0	0
Meropenem[3-6]	+++	0/+	0	++
Piperacillin/Tazobactam[4]	0	++++	0	+++
Cefepim[4]	0	+++	++	++
Aztreonam[4]	0	++	0	+++

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

MHK: minimale Hemmkonzentration

1. Takeda et al. *Antimicrob Agents Chemother.* 2007;51:826-30. 2. Crandon et al. *Antimicrob Agents Chemother.* 2012;56:6137-46. 3. Davies et al. *J Antimicrob Chemother.* 2011;66:2298-2307. 4. Livermore. *Clin Infect Dis.* 2002;34:634-40. 5. Riera et al. *J Antimicrob Chemother.* 2011;66:2022-7. 6. Zhanel et al. *Drugs.* 2007;67:1027-52.

Ceftolozan/Tazobactam Breakpoints

- EUCAST
  - >1mg/l Enterobakt und >4 mg/l Pseudomonas
  - Livermore: 8/4 oder 8/8mg/l ?

- CLSI

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)		
	S	I	R
Enterobacteriaceae	≤2/4	4/4	≥8/4
Pseudomonas aeruginosa	≤4/4	8/4	≥16/4
Streptococcus anginosus *Streptococcus constellatus* and *Streptococcus salivarius*	≤8/4	16/4	≥32/4
Bacteroides fragilis	≤8/4	16/4	≥32/4

S = susceptible, I = intermediate, R = resistant

Fachinfo
https://www.merck.com/product/usa/pi_circulars/z/zerbaxa/zerbaxa_pi.pdf
Livermore. JAC. 2010;65(9):1972–4

Ceftolozan/Tazobactam

- Studien
  - Compl. Intra-Abdominelle Infektion (c IAI)
    - Ceftolozan/Tazobactam versus Meropenem
  - Compl. Harnwegsinfektionen (c UTI)
    - Ceftolozan/Tazobactam versus Levofloxacin
      - Ceft/Tazo überlegen bei Heilungsrate und mikrobiolog. Eradikation

Ceftolozan/Tazobactam

ASPECT-cIAI*		
Primärer Endpunkt	**Ceftolozan/Tazobactam + Metronidazol**	**Meropenem**
Klin. Heilungsrate (mikrobiologische ITT-Population)	83,0%	87,3%
Sekundärer Endpunkt		
Klin. Heilungsrate ME-Population	94,2%	94,7%
ASPECT-cUTI		
Primärer Endpunkt	**Ceftolozan/Tazobactam**	**Levofloxacin**
Composite cure Rate in der mikrobiologischen modifizierten ITT-Population	76,9%	68,4%
Sekundärer Endpunkt		
Composite cure Rate in der Per-Protokoll-ITT-Population	83,3%	75,4%

ITT=intention to treat, ME=Mikrobiologisch evaluierbar
* Die Marge für Nichtunterlegenheit betrug 10%

Quellen: Solomkin et al. 2015, Wagenlehner et al. 2015

Real world (Österreich (AURES 2016) Pseudomonas (Blut, (Liquor))

AB	% Resistenz (Jahr 2016)
Ceftazidim	11,3%
PipTaz	13,8%
Carbapenem	12,9%
AG	6,1%
Chinolone	7,2%

99 Isolate mit V.a. Carbapenemaseproduktion ad Referenzlabor in Linz

→ 40,4% Carbapenamase-Gen nachweisbar

→ Metallo Betalaktamasen

Aures 2016.
Von
https://www.ages.at/download/0/0/dbc0e4bd9fbe48b96ce6ffe2f81a3bc83a964252/fileadmin/AGES2015/Themen/Arzneimittel_Medizinprodukte_Dateien/AURES/aures_2016.pdf

Real world (Österreich (AURES 2016)
Pseudomonas (nicht-invasiv, Ohr, Trachealsekret)

NG+KH		2012			2016			Vgl invasive Erreger
AB-Gruppe	**Material**	**N**	**%I**	**%R**	**N**	**%I**	**%R**	
Pip/Taz.	Ohrabstriche	1.261	0,9	6,7	1.339	0,0	4,6	13,8%
	Trachealsekret	760	0,0	23,9	852	0,2	22,2	
Ceftaz.	Ohrabstriche	796	0,5	1,0	1.308	0,0	4,2	11,3%
	Trachealsekret	748	0,0	19,1	841	0,2	19,5	
Ceph4	Ohrabstriche	1.267	0,2	3,0	1.235	0,0	3,1	
	Trachealsekret	753	0,0	14,5	809	0,2	15,4	
Aminogl.	Ohrabstriche	1.286	0,0	7,3	1.345	0,1	3,7	6,1%
	Trachealsekret	752	0,1	14,5	808	0,7	10,4	
Peneme	Ohrabstriche	796	2,1	2,0	1.301	2,2	4,3	12,9%
	Trachealsekret	758	4,5	18,9	838	6,8	17,2	
Cipro.	Ohrabstriche				1.349	1,9	6,2	7,2%
	Trachealsekret				853	4,5	14,9	

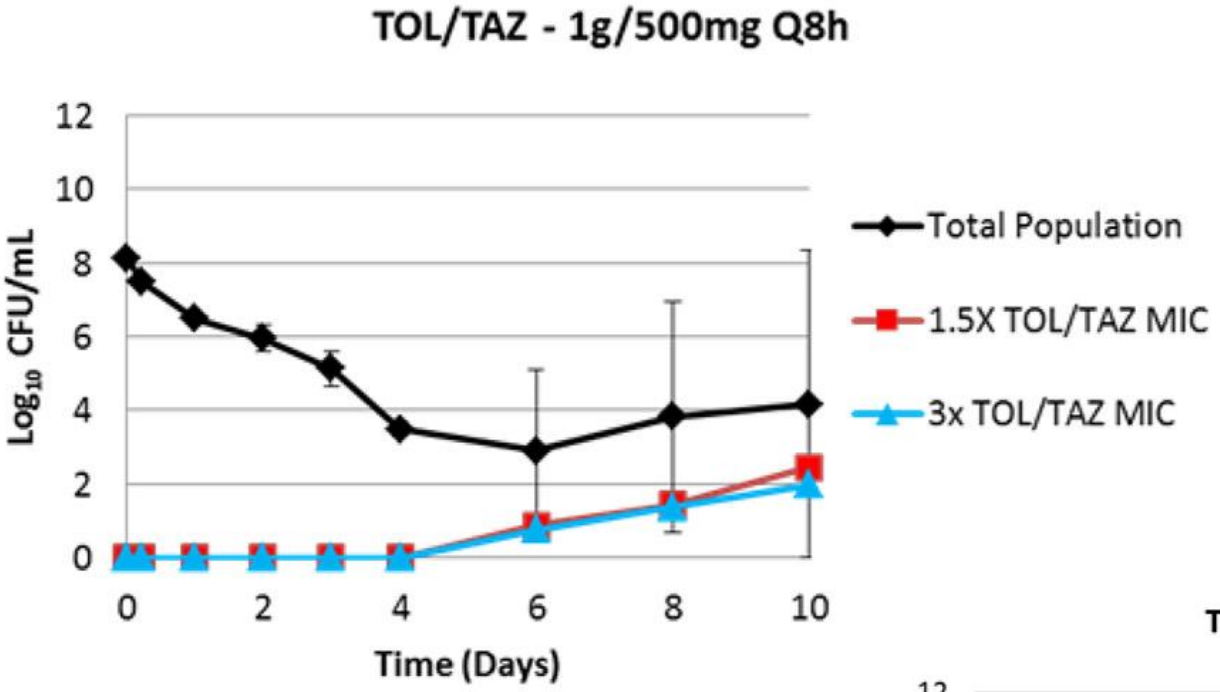
Von
https://www.ages.at/download/0/0/dbc0e4bd9fbe48b96ce6ffe2f81a3bc83a964252/fileadmin/AGES2015/Themen/Arzneimittel_Medizinprodukte_Dateien/AURES/aures_2016.pdf

Real world (Innere Medizin Graz) Pseudomonas aus Blutkulturen

***Pseudomonas aeruginosa* aus Blutkulturen (N=46)**

Substanz	**%R**	**%I**	**%S**
Piperacillin/Tazobactam	6,5	0	93,5
Ceftazidim	10,9	0	89,1
Cefepim	6,5	0	93,5
Aztreonam	10,9	89,1	0
Imipenem	17,4	0	82,6
Meropenem	17,4	2,2	80,4
Amikacin	2,2	2,2	95,7
Gentamicin	0	0	100
Tobramycin	2,2	0	97,8
Ciprofloxacin	13	0	87

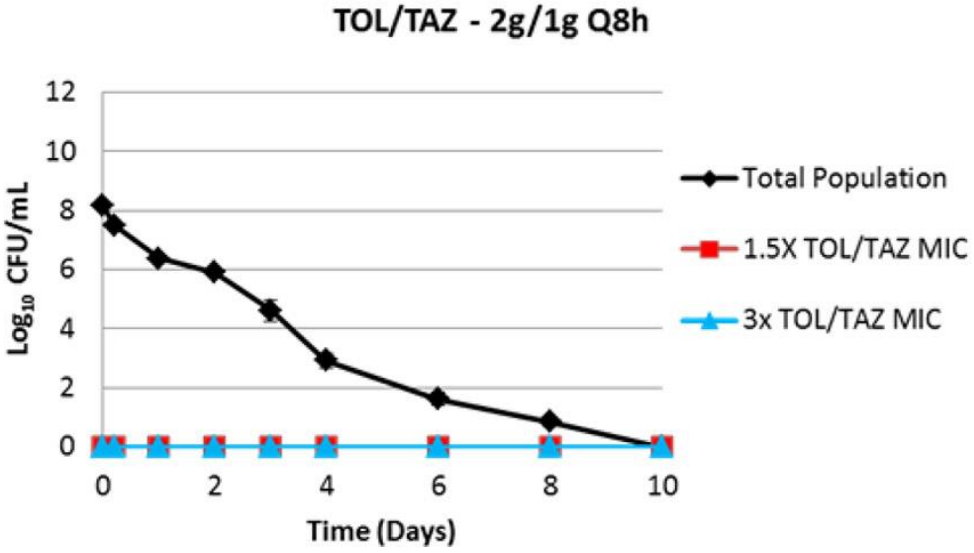
Dosis?



Klinisches Ps aeruginosa Isolat
(AMP C plus efflux Pumpe)
Ceftolozan /Tazobact MHK 4
PipTaz MHK 128

→ VAP Dosis

3x2/1g vs Ceftol/Taz vs. Meropenem



VanScoy. AAC 2014;58:6024

Ceftolozan/Tazobactam vs Meropenem bei NAP inkl VAP

- Ceftolozan/Tazobactam 3x3g iv
  - 2g Ceftolozan/1g Tazobactam
    - 50% Plasma ELF Konzentration[Lit1]
- Versus
- Meropenem 3x1g iv
- Beide plus empirisch Linezolid 2x600mg

1. Xiao. he Journal of Clinical Pharmacology 2016, 56(1) 56–66
2. https://www.clinicaltrials.gov/ct2/show/study/NCT02070757

Ceftolozan/Tazobactam vs Meropenem bei NAP inkl VAP

- Endpunkt erreicht
  - → non-inferiority to meropenem in day 28 all-cause mortality and in clinical cure rate

https://investors.merck.com/news/press-release-details/2018/Mercks-ZERBAXA-ceftolozane-and-tazobactam-Met-Primary-Endpoints-of-Non-Inferiority-Compared-to-Meropenem-in-Pivotal-Phase-3-Study-of-Adult-Patients-with-Hospital-Acquired-Bacterial-Pneumonia-or-Ventilator-Associated-Bacterial-Pneumonia/default.aspx

Cefto/Tazo: "Real-World" Experience – **ECCMID 2018**

Citation	Study Type	N	Infection Type(s)	ICU (n)	Immuno-compromised (n)	Clinical/Micro Cure	30-day All Cause Mortality	Region
Jorgensen (Rybak) #P0286	Retrospective, multicenter	99	Mixed (66% RTI; additional details ND)	ND	ND	ND (32% composite failure)	14%	US
Gioia #P0287	Single center, retrospective	15	Mixed MDR PsA (53% RTI, 27% IAI, 13% Wound, 1 BSI)	8 (53%)	9 (60%)	60%	27% (4/15)	Spain (U Hosp Ramony Cajal, Madrid)
Tordato #P0289	Single center, retrospective	11	Mixed (54% RTI, 27% BSI, 18% IAI)	6	3 HSCT	100%	36% (4/11)	Italy
Gallagher #P0290	Retrospective, multicenter (n=11)	133	Mixed MDR PsA (63% RTI, 10% UTI, 9% IAI, 8% wound, 7% BJI, 3% 1° BSI)	86 (76%)	ND	76%	20%	US (PA, MD, IN, NJ, NY)
Jayakumar #P0669	Retrospective, multicenter (n=2)	22	Sepsis and/or bacteremia	ND	ND	77%	23%	US (NV)
Pogue #O0740	Retrospective, IDN database	103	PsA cUTI (64%) & cIAI (36%)	ND	ND	ND	14%	US

Rybak – Composite failure – 30-d mortality, 30-d recurrence – failure to resolve temp & WBC.
Fernandez-Cruz – Controls tx: COL, AMK, P/T, MER, CIP as per susceptibility

Posters/Posterabstracts available: *http://m.eccmidlive.org/#Abstracts*

Published RWE with Cefto/Tazo 1 (case reports excl)

Citation	Study Type	N	Infxn Type(s)	ICU (n)	Immuno Comp (n)	Micro Data	Findings / Results	Region
Caston JJ et al. AAC 2017; 61(3). Pii: e02136-16.	Retro-spective, multi-center, compa-ssionate use	12	RTI (6) IAI (3) Otitis & mastoiditis (1) Biliary (1) Central catheter (1) 5 bld cx+	ND 10 had "Septic shock" and 1 had "severe sepsis"	4	MDR **PsA** (R to ≥3 Abx: FEP, P/T, MERO, CIP, AMG); 8 were S to COL. All initial PsA were S to C/T	In 10 pts (83.3%), micro eradication was observed 30 d after C/T EOT. However, 2 pts had C/T-R MDR PsA in cx's taken subsequent to this period (MIC 48 in both) All cause mortality in 3/12 (25%).	Spain
Haidar G et al. CID 2017	Case series	21	RTI (18) (6 w/CF) BSI (1) cIAI (1) cUTI (1)	ND[a]	9	All MDR **PsA** (15 initial m/o were R to all BL) All initial isolates were C/T S	C/T tx success was 71% BSI – success, died within 90 d (not attributable) cIAI – clinical success; colonized at 90d cUTI – clinical success; colonization at 90d 30-d all cause & attributable mortality: 10% (2/21) & 5% (1/21) 90-d all cause & attributable mortality: 48%(10/21) & 19% (4/21) Resistance emerged in 3 pts	US (PA)
Dinh A et al. IJAA 2017; 49: 782-3	Retro-spective study of early access	15	UTI (3) RTI (7) IAI (2) CNS (1) BJI (1)	8	10	XDR-**PsA** (NS to all but 2 or fewer Abx categories). All were S to C/T	Clinical cure was 67% (10/15). All-cause in-hospital mortality was 27% (4/15), including 1 clinical failure. No C/T resistant strains were isolated.	France

Published RWE with Cefto/Tazo 2 (case reports excl)

Citation	Study Type	N	Infxn Type(s)	ICU (n)	Immuno Comp (n)	Micro Data	Findings / Results	Region
Dietl, 2017 Int Jour of Antimicr Agents	Retrospective, single center, case series	7	43% SSTI 57% Osteomyelitis	-	-	MDR **PsA**	86% clinical cure, 1 patient experienced recurrence, 57% microbiological eradication 2 pat C/T salvage therapy due to kidney failure	Spain
Katchanov, 2017, Plos One	Retrospective, single center, case series	119	-	68	32	**PsA** in 55.5%	3 pat treated w/ C/T, 5 w/ Caz/Avi, carbapenemase genes identified	Germany

Published RWE with Cefto/Tazo 3(case reports excl)

Citation	Study Type	N	Infxn Type(s)	ICU (n)	Immuno Comp (n)	Micro Data	Findings / Results	Region
Hakki Infection 2018	Retrospective, single center, case series	6	7 episodes* (6 patients) MDR PsA (3 RTI, 3 BSI, 1 soft tissue)	ND	6 (100%) hematologic malignancies or undergone HCT	MDR **PsA**	83% Clinical cure, prolonged therapy, 2 clinical failures, 1 resistance development	US
Escola-Verge Infection 2018	Retrospective, single center	38	Mixed XDR PsA (14 RTI, 6 Skin, 6 UTI, 4 bone, 4 IAI, 3 BSI, 1 mediastinitis) 11 bacteremic	12 (31%)	20 (53%) steroids, 29% SOT, 3% HOT, 16% chemo, 16% ANC<500	MDR **PsA** (S to colisitin)	Clinical Cure: 87% (EOT), 68% (90-d), wound management and high dose of C/T important for clinical success	Spain
Diaz-Canestro EJCMID 2018	Prospective, observational single center study	58	Mixed (60% pneumonia) 97% MDR PsA	16 (28%)	7 (12%)	86% XDR **PsA** (S to colisitin and amikacin)	64% Clinical cure, resistance mechanism described: AmpC	Spain
Xipell M J Glob Antimicrob Resist 2018	Retrospective, single center	23	23 pts with 24 episodes of MDR-PsA (8 RTI, 6 SSTI, 7 UTI, 3 IAI)	ND	10 (43%)	MDR-**PsA**	Clinical cure: 88%	Spain

Published RWE with Cefto/Tazo 4 (case reports excl)

Citation	Study Type	N	Infxn Type(s)	ICU (n)	Immuno Comp (n)	Micro Data	Findings / Results	Region
Dietl, 2017 Int Jour of Antimicr Agents	Retrospective, single center, case series	7	43% SSTI 57% Osteomyelitis	-	-	MDR PsA	86% clinical cure, 1 patient experienced recurrence, 57% microbiological eradication 2 pat C/T salvage therapy due to kidney failure	Spain
Katchanov, 2018, Plos One	Retrospective, single center, case series	119	-	68	32	PsA in 55.5%	**3 pat treated w/ C/T, 5 w/ Caz/Avi, carbapenemase genes identified**	Germany

Hamburg (Katchanov Plos One 2018)

- Retrospektive Studie
- Daten von Pat mit Carbapenem resist Kolonisation/Infektion
- 3 Pat ABx Th mit Ceftolozan/Tazobactam
  - Ps. aeruginosa
- 5 Pat ABx Th mit Ceftazidim/Avibactam
  - Kl pneumoniae

- Alle Pat mit Grunderkrankungen
  - CF, TX, IBD, Ö Fistel, etc
  - 1 Pat hat überlebt

Katchanov. PLoS ONE 13 (4): e0195757

Aktivität verschiedener β-Lactamase-Inhibitoren

	β-Lactamase-Enzyme					
	AmpC	**CTX-M**	**SHV**	**TEM**	**KPC**	**MBL**
Sulbactam[3]	-/+[a]	+	+	+	-	-
Clavulansäure[4,5]	-	+	+	+	-	-
Tazobactam[3,6]	-	+	+	+	-	-
Avibactam[7]	+	+	+	+	+	-

Ceftazidim/Avibactam

1. Livermore et al. *J Antimicrob Chemother*. 2010;65:1972-4. 2. Titelman et al. *Diag Microbiol Infect Dis.* 2011;70:137-41. Drawz and Bonomo. *Clin Microbiol Rev.* 2010;23:160-201. 4. Jacoby and Munoz-Price. *N Engl J Med.* 2005;352:380-91. 5. Shahid et al. *Crit Rev Microbiol.* 2009;35:81-108. 6. Data on file, Cubist Pharmaceuticals. el et al. *Drugs.* 2013;73:159-77.

Ceftazidim/Avibactam 3x2,5g Zavicefta

- Komplizierte intraabdominelle Infektionen (cIAI)
- Komplizierte Harnwegsinfektionen (cUTI), einschließlich Pyelonephritis
- Nosokomiale Pneumonien (HAP), einschließlich beatmungsassoziierter Pneumonien (VAP)

- Zavicefta ist auch indiziert für die Behandlung von Infektionen aufgrund aerober Gram-negativer Erreger bei erwachsenen Patienten mit begrenzten Behandlungsoptionen

https://ec.europa.eu/health/documents/community-register/2016/20160624135109/anx_135109_de.pdf

Ceftazidim/Avibactam 3x2,5g Zavicefta

- Komplizierte intraabdominelle Infektionen (cIAI)
  - Ceftaz/Avibactam plus Metron versus **Meropenem 3x1g iv**
- Komplizierte Harnwegsinfektionen (cUTI), einschließlich Pyelonephritis
  - versus **Doripenem 3x500mg**
- Nosokomiale Pneumonien (HAP), einschließlich beatmungsassoziierter Pneumonien (VAP)
  - versus **Meropenem 3x1g iv**
  - **Plus** open label Linezolid (oder Vancomycin) plus Aminglycosid (außer bei KI)
    - 56-61% bis 72h, 21-24% >72h Aminoglycosid

- Zavicefta ist auch indiziert für die Behandlung von Infektionen aufgrund aerober Gram-negativer Erreger bei erwachsenen Patienten mit begrenzten Behandlungsoptionen
  - Ceftazidim plus Metron versus „best available Therapy“

https://ec.europa.eu/health/documents/community-register/2016/20160624135109/anx_135109_de.pdf
Torres. Lancet Infect Dis 2018; 18: 285–95

Meta-analyse Caz/Avi

- 12 Studien mit 4591 Patienten

- → Caz/Avi ist vergleichbar effektiv wie Carbapenem zur Behandlung von Infektionen mit Gram negativen Erregern
  - Meist Enterobakterien
    - Ps. aeruginosa in Zulassungsstudien
  - cIAI, cUTI, bacteremia, HAP

  - Observative (1x prospektive, 2x retrospektive) **real world evidence** nur bei Enterobakterien

Zhong et al. Int J Antimicrob Agents. 2018;0:1–8.

Table 1
Characteristics of the included studies

Source	Region	Design	No. (I/C)	Mean age (years) (I/C)	Sex (% female)	Type of infection	Causative pathogen(s)	Concomitant therapy	Dosage	Comparator/dosage	Antimicrobial duration	Outcomes
Vazquez et al., 2012 [30]	Multicentre (global)	RCT	68/67	46/48	75/73	cUTI	Mix	None	CAZ 500 mg + AVI 125 mg q8h	IPM-CIL 500 mg q6h	7–14 days	Clinical response, microbiological response, AEs and SAEs
Lucasti et al., 2013 [29]	Multicentre (global)	RCT	101/102	43/43	31/21	cIAI	Mix	MTR	CAZ 2000 mg + AVI 500 mg q8h	MEM 1000 mg q8h	5–14 days	Clinical response, microbiological response, AEs, SAEs and mortality
Carmeli et al., 2016 [28]	Multicentre (global)	RCT	165/168	63/62	45/45	cUTI and cIAI	CAZ-NS Enterobacteriaceae and PA	None	CAZ 2000 mg + AVI 500 mg q8h	Best available therapy (CB, COL and TIG, combination)	5–21 days	Clinical response, microbiological response, AEs and SAEs
Wagenlehner et al., 2016 [17]	Multicentre (global)	RCT	393/417	51/53	69/70	cUTI	Mix	None	CAZ 2000 mg + AVI 500 mg q8h	DOR 500 mg q8h	5–14 days	Clinical response, microbiological response, AEs, SAEs and mortality
Mendes et al., 2016 [26]	Multicentre (global)	RCT	86/90	N/A	N/A	cUTI and cIAI	GNB	MTR for cIAI	CAZ 500 mg + AVI 125 mg q8h for cUTI; CAZ 2000 mg + AVI 500 mg q8h for cIAI	IPM-CIL 500 mg q6h; MEM 1000 mg q8h	5–14 days	Clinical response, microbiological response
Mazuski et al., 2016 [27]	Multicentre (global)	RCT	520/523	50/50	37/36	cIAI	Mix	MTR	CAZ 2000 mg + AVI 500 mg q8h	MEM 1000 mg q8h	5–14 days	Clinical response, microbiological response, AEs, SAEs and mortality
Mendes et al., 2017 [24]	Multicentre (global)	RCT	413/410	N/A	N/A	cIAI	Aerobic GNB	MTR	CAZ 2000 mg + AVI 500 mg q8h	MEM 1000 mg q8h	5–14 days	Clinical response
Qin et al., 2017 [23]	Multicentre (Asia)	RCT	214/217	48/48	34/30	cIAI	Mix	MTR	CAZ 2000 mg + AVI 500 mg q8h	MEM 1000 mg q8h	5–14 days	Clinical response, AEs, SAEs and mortality
Torres et al., 2018 [18]	Multicentre (global)	RCT	356/370	62/62	25/26	HAP	Mix	None	CAZ 2000 mg + AVI 500 mg q8h	MEM 1000 mg q8h	7–14 days	Clinical response, microbiological response, AEs, SAEs and mortality
Castón et al., 2017 [25]	Multicentre (global)	Retrospective study	8/23	61/59	50/35	Bacteraemia	CRE	N/A	CAZ 2000 mg + AVI 500 mg q8h, doses adjusted according to renal function	Other treatments (CB, AG, BLIBL, TIG, FOS, COL)	N/A	Clinical response and mortality
Shields et al., 2017 [22]	Single centre (USA)	Retrospective study	13/90	66/60	46/43	Bacteraemia	CRKP	GEN	N/A	CB+AG, CB+COL, other treatments	N/A	Clinical response, AEs, SAEs and mortality
van Duin et al., 2018 [16]	Multicentre (USA)	Prospective observational study	38/99	57/63	39/58	Mix	CRE	TIG, AG, GEN, CB, FOS, SXT	N/A	COL	N/A	Clinical response, AEs and mortality

I/C, intervention/control; RCT, randomised controlled trial; cUTI, complicated urinary tract infection; CAZ, ceftazidime; AVI, avibactam; q8h, every 8 h; IPM-CIL, imipenem/cilastatin; q6h, every 6 h; AEs, adverse events; SAEs, serious adverse events; cIAI, complicated intra-abdominal infection; MTR, metronidazole; MEM, meropenem; CAZ-NS, ceftazidime-non-susceptible; PA, *Pseudomonas aeruginosa*; CB, carbapenems; COL, colistin; TIG, tigecycline; DOR, doripenem; N/A, not available; GNB, Gram-negative bacteria; HAP, nosocomial pneumonia; CRE, carbapenem-resistant Enterobacteriaceae; AG, aminoglycosides; BLIBL, β-lactamase-inhibiting β-lactams; FOS, fosfomycin; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; GEN, gentamicin; SXT, trimethoprim/sulfamethoxazole.

Ceftazidim/Avibactam real world

- Van Duin CID 2018;66(2):163–71
  - Observative Studie
  - 38 Pat mit Caz/Avi versus 99 Pat mit Colistin
    - Carbapenem resistente **Enterobakterien**
      - 33% versus 8% Tod 30 Tage nach Therapiebeginn
- Shields AAC 2017;61:e00883-17
  - Observative Studie
  - 13 Pat Caz/Avi, 25 Pat Carba+AG, 30 Pat Carba+Col, 41 Pat andere Therapie
    - Carbapenem resistente **Enterobakterien**
      - 85%, 48%, 40%, 37% Therapierfolg Tag 30
- Caston Int J of Infectious Diseases 2017;59:118–123
  - Observative Studie
  - 8 Pat Caz/Avi, 23 Pat andere Therapie; hämatolog Pat.
    - Carbapenem resistente **Enterobakterien**
    - 85,7% versus 34,8% Überleben

Resistenzen

- 42 Carbapenem resistente Pseudomonas aeruginosa Isolate
- In vitro

Wi. AAC 2017;62:e01970-17.

Ps. aeruginosa Resistenz gg. Ceftolozan/Tazobactam oder Ceftazidim/Avibactam

Resistance mechanism	No. of isolates	MIC range (median) (mg/liter)		% resistance	
		Ceftolozane-tazobactam	Ceftazidime-avibactam	Ceftolozane-tazobactam	Ceftazidime-avibactam
Decreased *oprD* expression	13	1–16 (2)	2–16 (4)	7.7	15.4
Decreased *oprD* and increased *mexB* expression[a]	9	1–4 (2)	2–32 (16)	0	55.6
Decreased *oprD* and increased *mexY* expression	1	1	2	0	0
Decreased *oprD* and increased *ampC* expression	3	1–4 (2)	4–8 (4)	0	0
Decreased *oprD* and increased *mexB* and *ampC* expression	4	2–32 (4)	8–16 (16)	25.0	50.0
Decreased *oprD* and increased *mexY* and *ampC* expression	1	2	16	0	100
Decreased *oprD* and increased *mexB*, *mexD*, and *ampC* expression	6	1–4 (2)	2–8 (4)	0	0
Decreased *oprD* and increased *mexB*, *mexY*, and *ampC* expression	2	2	8	0	0
Increased *mexB* expression	2	2	8–16	0	50
Increased *mexY* and *ampC* expression	1	4	16	0	100

[a]$P < 0.05$ in comparison of percent resistance to ceftolozane-tazobactam with that to ceftazidime-avibactam.

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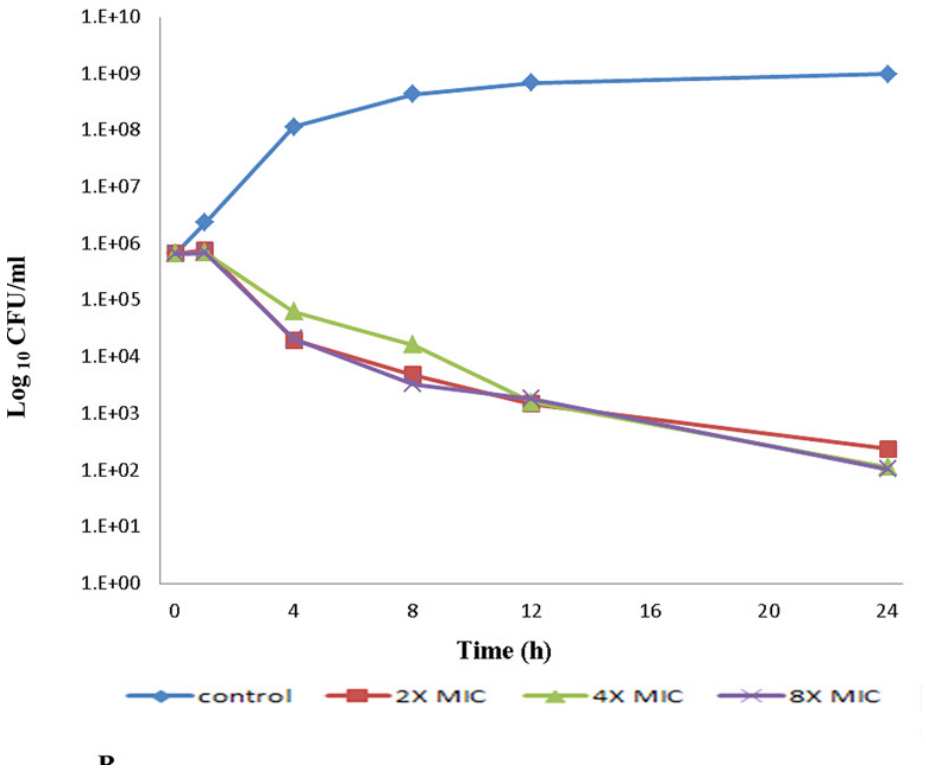
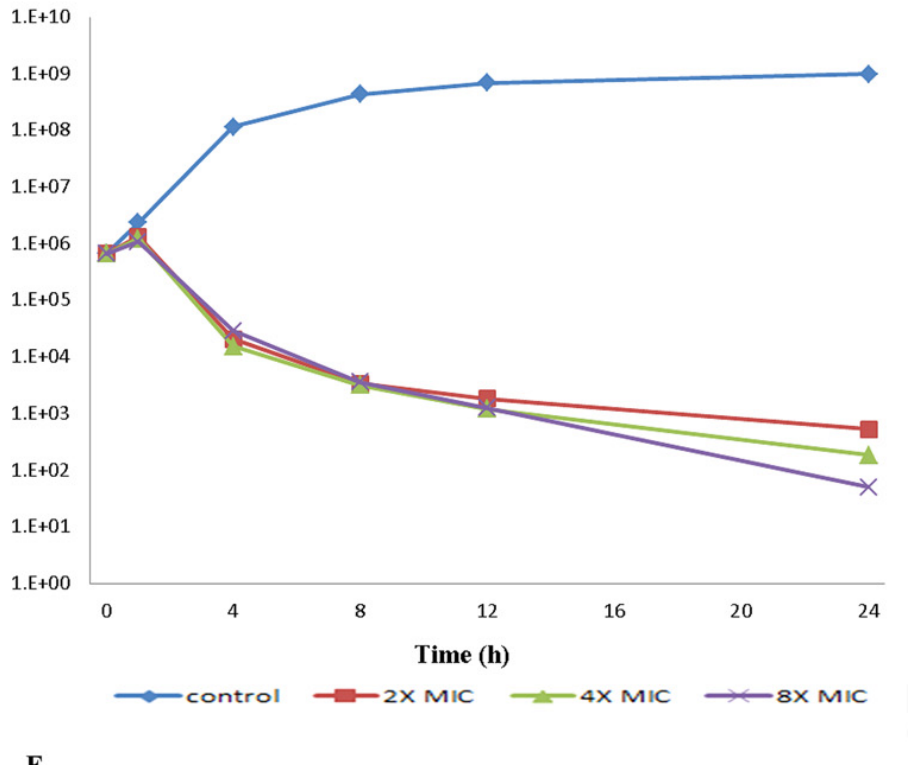
Ps. aeruginosa Resistenz gg. Ceftolozan/Tazobactam oder Ceftazidim/Avibactam

downregulated *oprD* and upregulated *mexB* Ps. aeruginosa *isolate*

Ceftolozan/Tazobactam



CeftazidimTAvibactam



Wi. AAC 2017;62:e01970-17.

Zusammenfassung
Neue BL/BLI bei Nonfermentern

- Ceftolozan/Tazobactam
  - Wertvolle Therapiemöglichkeit
    - cIAI, cUTI
    - NAP inkl VAP (3x3g iv) (Studie abgeschlossen, Zulassung noch fehlend)
  - In vitro besser als Ceftazidim/Avibactam

- Ceftazidim/Avibactam
  - Wertvolle Therapiemöglichkeit bei Enterobakterien
  - Weniger wirksam bei Penem-resistenten Nonfermentern vgl mit Ceftolozan Tazobactam