

Efficacy of Ceftazidime-Avibactam Salvage Therapy  
in Patients With Infections Caused by *Klebsiella*  
*pneumoniae* Carbapenemase-producing *K.*  
*pneumoniae*

Tumbarello M et. Al, CID 2019;68(3): 355-64

Journal Club 28.01.2019

# Ausgangslage

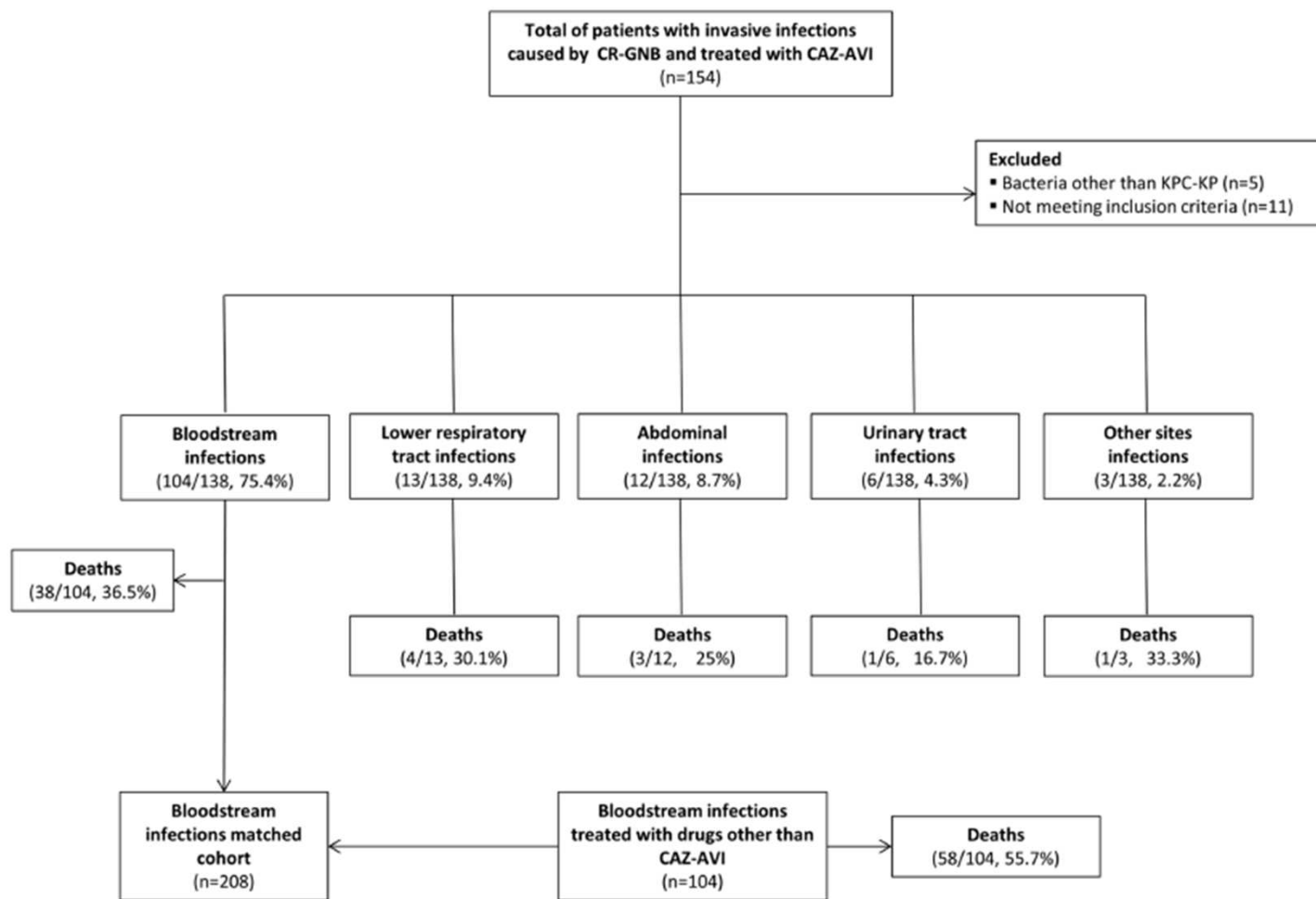
- Ceftazidime/Avibactam (CAZ/AVI) seit 2016 in EU zugelassen für:
  - Komplizierte intraabdominale Infektionen
  - Komplizierte Harnwegsinfektionen
  - Hospital-acquired Pneumonia (inkl. VAP)
  - Aerobe gram-negative Infektionen mit Therapieeinschränkungen (v.a. Carbapenem-resistente Enterobacteriaceae)
- In-vitro Wirksamkeit bei KPC aber auch ESBL, AmpC und Oxacillinase
- Wenige Daten bezüglich Wirksamkeit in-vivo
- Vergleich gegen Carbapeneme in Zulassungsstudien

# Studien-Design

- Retrospektive Beobachtungsstudie in 17 Kliniken in IT 04/16 – 12/17
- CAZ/AVI Salvage Therapie im Rahmen Compassionate-use
- Einschluss-Kriterien
  - >18j, Kultur-bestätigte KPC *K. pneumoniae* Infektion, >72h Therapie mit CAZ/AVI 2.5g i.v. alle 8h
- Primärer Endpunkt: 30 Tage Mortalität
- Sekundärer Endpunkt: Wirksamkeit von CAZ/AVI bei KPC *K.pneumoniae* Bakteriämien (case-control matching)

# Definitionen

- Bakteriämie: positive Blutkulturen und SIRS
- Nicht-bakteriämie Infektionen: Kultur-Nachweis nicht in BK, persistierend negative BK und klinische Infektionszeichen
- Kombinationstherapie: CAZ/AVI plus  $\geq 1$  KPC-aktives AB für 3d
- Relapse: Zweite KPC *K. pneumoniae* Infektion während Hospitalisation
- High-Risk Bakteriämien: unklarer Infektfokus oder Fokus ausserhalb des Urogenitaltraktes resp. Gallenwege



**Figure 1.** Flowchart of patients' inclusion process. Abbreviations: CAZ-AVI, ceftazidime-avibactam; CR-GNB, carbapenem-resistant Gram-negative bacteria; KPC-Kp, *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*.

**Table 1. Characteristics of Patients With Ceftazidime-Avibactam–treated *Klebsiella pneumoniae* Carbapenemase–producing *K. pneumoniae* Infections**

Variable	All Infections (N = 138)	Bacteremic Infections (n = 104)	Nonbacteremic Infections (n = 34)	P Value
<b>Patient variables</b>				
Male sex	94 (68.1)	68 (65.4)	26 (76.5)	.23
Age, y, median (IQR)	60 (25–79)	61 (27–79)	57 (25–79)	.31
<b>Comorbidities</b>				
COPD	12 (8.7)	10 (9.6)	2 (5.9)	.50
Cardiovascular disease	51 (36.9)	43 (41.4)	8 (23.5)	.06
Cerebrovascular disease or dementia	15 (10.9)	8 (7.7)	7 (20.6)	.03
Solid tumor	27 (19.6)	19 (18.3)	8 (23.5)	.50
Hematologic malignancy	19 (13.7)	15 (14.4)	4 (11.7)	.69
Liver disease	25 (18.1)	19 (18.3)	6 (17.6)	.93
SOT	35 (25.4)	28 (26.9)	7 (20.6)	.46
Chronic renal failure	35 (25.4)	27 (25.9)	8 (23.5)	.77
Diabetes mellitus	22 (15.9)			
Neutropenia	15 (10.9)			
Charlson comorbidity index ≥3	47 (34.1)			
<b>Ward submitting index culture</b>				
Medical (all)	60 (43.5)			
Hematology	9 (6.5)			
Surgical (all)	32 (23.2)			
Transplantation	7 (5.1)			
ICU	46 (33.3)			
<b>Preinfection healthcare interventions</b>				
Surgery <sup>a</sup>	60 (43.5)			
Dialysis <sup>a</sup>	15 (10.9)			
Endoscopy <sup>a</sup>	21 (15.2)			
Mechanical ventilation <sup>b</sup>	43 (31.2)			
<b>Indwelling invasive devices</b>				
Central venous catheter	108 (78.3)			
Bladder catheter	100 (72.5)			
Nasogastric tube <sup>c</sup>	56 (40.6)			
Surgical drain <sup>d</sup>	45 (32.6)			
<b>Infection variables</b>				
Polymicrobial	12 (8.7%)			
Healthcare-associated	16 (11.6)			
Hospital-acquired	122 (88.4)			
Septic shock <sup>e</sup>	43 (31.2)			
<b>Treatment variables</b>				
<b>Antibiotic regimens prior to CAZ-AVI salvage therapy</b>				
Colistin plus tigecycline	31 (22.5)			
Colistin plus tigecycline plus meropenem	28 (20.3)			
Double carbapenem	18 (13.1)			
Fosfomycin plus tigecycline	16 (11.6)			
Colistin	12 (8.7)			
Colistin plus meropenem	8 (5.7)			
Gentamicin plus tigecycline	8 (5.7)			
Other	13 (9.4)			
Days before CAZ-AVI treatment, median (IQR)	7 (3–10)			
CAZ-AVI combined with	109 (78.9)			
Noncarbapenem drugs <sup>d</sup>	88/109 (80.7)	63/82 (76.8)	25/27 (92.6)	.07
Carbapenems <sup>d</sup>	21/109 (19.3)	19/82 (23.17)	2/27 (7.4)	.07
Days of CAZ-AVI treatment, median (IQR)	14 (4–41)	14 (3–28)	15 (6–55)	.18
<b>Outcomes</b>				
30-d mortality	47 (34.1)	38 (36.5)	9 (26.5)	.28
Infection relapse <sup>e</sup>	12 (8.7)	10 (9.6)	2 (5.9)	.50

## Anmerkungen zum Outcome der Salvage Therapie

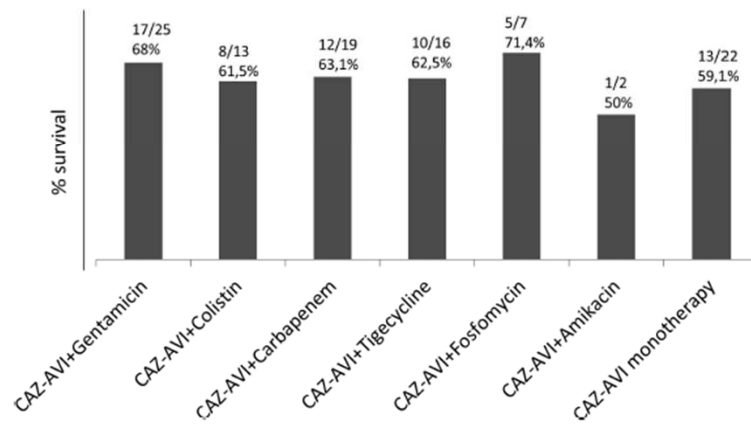
- 2.2% (n=3) hatten persistierend positive Kulturen (2 BK, 1 Lunge) bei neuer in-vitro Resistenz gegen CAZ/AVI
- 2/3 unter CAZ/AVI Monotherapie, 1 davon an Dialyse
- 8.7% (n=12) Rückfälle nach CAZ/AVI Therapie (10 BK, 1 HWI, 1 Lunge)

**Table 2. Characteristics of Patient Groups<sup>a</sup> Whose *Klebsiella pneumoniae* Carbapenemase-producing *K. pneumoniae* Bacteremic Infections Were Treated with Ceftazidime-Avibactam-containing Salvage Regimens (Cases) or Alternative Salvage Regimens (Controls)**

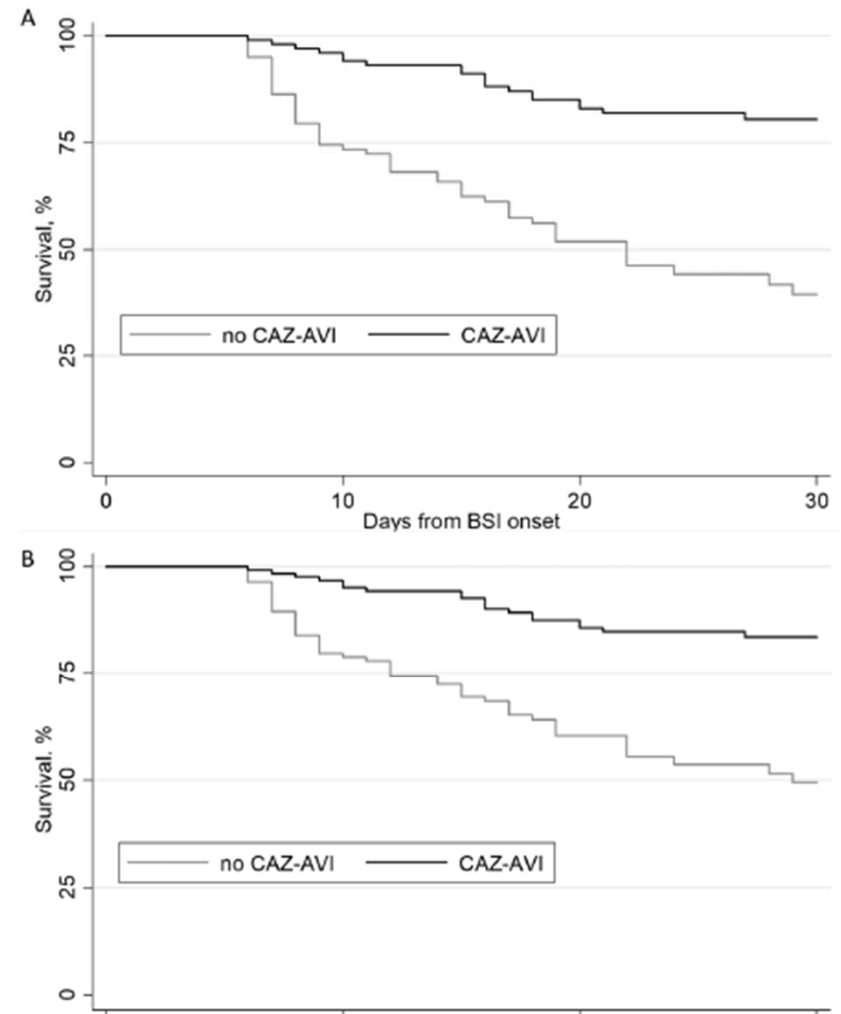
Characteristic	Cases (n = 104)	Controls (n = 104)	P Value
<b>Patient variables</b>			
Male sex	68 (65.4)	67 (64.4)	.88
Age, y, median (IQR)	60 (27–79)	72 (53–85)	<.001
<b>Comorbidities</b>			
COPD	10 (9.6)	11 (10.6)	.82
Cardiovascular disease	43 (41.3)	59 (56.7)	.02
Cerebrovascular disease or dementia	8 (7.7)	15 (14.4)	.12
Solid tumor	19 (18.3)	15 (14.4)	.45
Hematologic malignancy	15 (14.4)	16 (15.4)	.84
Liver disease	19 (18.3)	10 (9.6)	.07
Solid organ transplant recipient	28 (26.9)	14 (13.5)	.01
Chronic renal failure	27 (25.9)	30 (28.8)	.64
Diabetes	20 (19.2)	28 (26.9)	.18
Neutropenia	13 (12.5)	14 (13.5)	.84
Charlson comorbidity index >3	38 (36.5)	28 (26.9)	.14
<b>Ward submitting index culture</b>			
Medical (all)	42 (40.4)	55 (52.8)	.07
Hematology	6 (5.8)	13 (12.5)	.09
Surgical (all)	23 (22.1)	20 (19.2)	.61
Organ transplants	5 (4.8)	2 (1.9)	.25
ICU	39 (37.5)	27 (25.9)	.07
<b>Infection variables</b>			
Healthcare-associated	10 (9.6)	11 (10.6)	.81
Hospital-acquired	94 (90.4)	91 (87.5)	.51
High-risk BS <sup>b</sup>	64 (61.5)	74 (71.2)	.14
Colistin-resistant KPC-Kp isolate	84 (80.7)	89 (85.6)	.85
<b>Clinical status<sup>c</sup></b>			
Septic shock	3		
Pitt score, median (IQR)			
<b>Salvage therapy variables</b>			
Days before salvage therapy, median (IQR)	7 (3–9)	7 (3–9)	.36
Monotherapy	22 (21.2)	27 (25.9)	.41
Combination therapy	82 (78.8)	77 (74.3)	.41
<b>Outcomes</b>			
30-d mortality	38 (36.5)	58 (55.8)	.005
Infection relapse <sup>d</sup>	10 (9.6)	9 (8.6)	.81



# 30-Tages Mortalität



A: Überleben CAZ/AVI vs. Andere Therapie  
B: Überleben CAZ/AVI vs. Andere Therapie nach Korrektur für septischen Schock



# Risikofaktoren für Mortalität

**Table 4. Multivariate Analysis of Factors Associated With 30-Day Mortality in the 208 Patients With *Klebsiella pneumoniae* Carbapenemase–producing *K. pneumoniae* Bacteremia**

Variable	Without Propensity Score Adjustment		Adjusted for the Propensity Score for Therapy With CAZ-AVI	
	P Value	OR (95% CI)	P Value	OR (95% CI)
Mechanical ventilation	<.001	4.25 (1.99–9.09)	<.001	4.31 (1.99–9.33)
Charlson comorbidity index $\geq 3$	.001	3.31 (1.61–6.77)	.001	3.30 (1.61–6.77)
Neutropenia	.01	3.22 (1.25–8.29)	.03	3.36 (1.25–8.75)
Septic shock	.002	2.95 (1.46–5.94)	.003	2.94 (1.46–5.92)
Any regimen that included CAZ-AVI	<.001	0.25 (.13–.51)	.001	0.27 (.13–.57)

Abbreviations: CAZ-AVI, ceftazidime-avibactam; CI, confidence interval; OR, odds ratio.

# Diskussion

- Steigende Anzahl an KPC *K. pneumoniae* Infektionen aber wenig Daten über Therapiemöglichkeiten
- CAZ/AVI als mögliche gute Alternativtherapie in Endemieregionen
- Eingeschränkte Aussagekraft da retrospektive Studie und compassionate-use
- Möglicherweise weniger Resistenzentwicklung bei Bakteriämien als bei Pneumonien
- 30-Tage Mortalität kann mit CAZ/AVI deutlich gesenkt werden

# Antibiotische Therapie Kontroll-Gruppe

- **Antibiotic regimens** Total (%)
- Double carbapenem 29 (27.9)
- Gentamycin 14 (13.5)
- Fosfomycin plus amikacin 13 (12.5)
- Fosfomycin plus gentamycin 11 (10.5)
- Gentamycin plus meropenem 11 (10.5)
- Colistin plus fosfomycin 10 (9.6)
- Colistin 9 (8.6)
- Others 7 (6.7)