Clinical Infectious Diseases

MAJOR ARTICLE

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

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Journal Club 16.08.2021

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Hintergrund

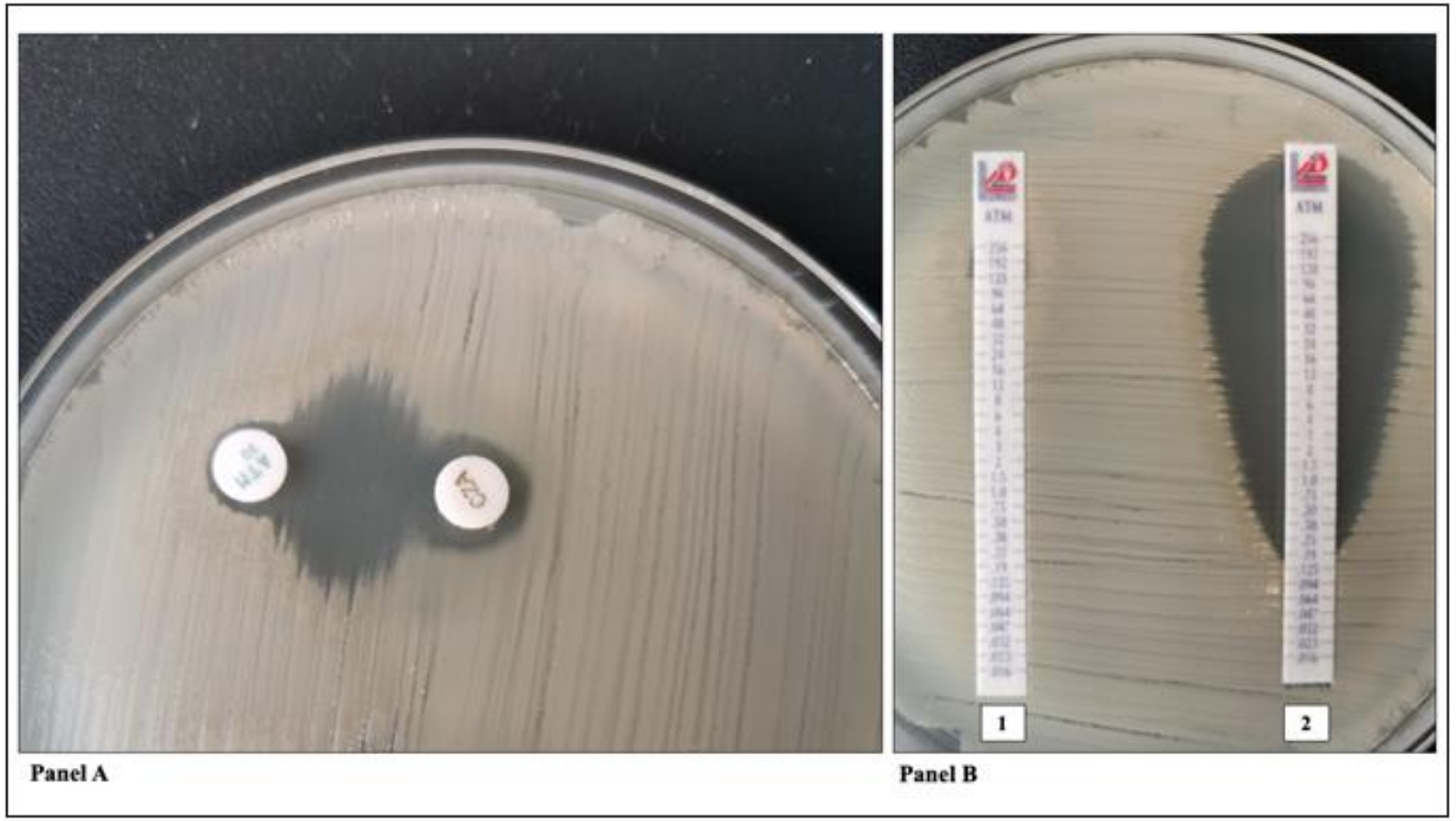
- Zunahme der Metallo-β-lactamase (MBL) produzierenden Enterobacterales in Europa und weltweit
- Mortalität bei Bakteriämie > 30%
- NDM, VIM und IMP inaktivieren alle β-Lactame ausser Aztreonam
- Optimale Therapie bei Bakteriämien mit MBL ist unklar
- Mögliche Alternativtherapie: Ceftazidim/Avibactam und Aztreonam

Methodik (1)

- Observationelle, prospektive Studie
- Dauer: Nov. 2018 – Dez 2019

- Einschlusskriterien: >18j, positive Blutkulturen mit MBL-produzierenden Enterobacterales, Therapie mit ≥1 in-vitro wirksamen Antibiotikum für min. 48h
- Follow-up: Bis Tag 30 nach der Bakteriämie

Synergie-Testung



Panel A: double-disk synergy test - distance of 20 mm from each other (center to center); **Panel B**: gradient-test superposition method (**1**: ATM strip applied in a place without CAZ-AVI; **2**: ATM strip applied in the position where CAZ-AVI was previously placed)

Endpunkte

- Primärer Endpunkt:
  - 30-Tage all-cause Mortalität
- Sekundäre Endpunkte:
  - Klinisches Therapieversagen an Tag 14
  - Hospitalisationsdauer nach Bakteriämie

Resultate

- 107 Bakteriämien im Studienzeitraum dokumentiert
- 102 Patienten eingeschlossen
  - NDM: *K. pneumoniae (n=79), E. coli (n=3)*
  - VIM: *K. pneumoniae (n=14), Enterobacter spp (n=5), M. morganii (n=1)*

Table 1. In Vitro Susceptibilities of 102 Metallo-β-Lactamase–Producing Blood Isolates

	MIC, mg/L	Susceptibility Rate, %	
Bacterial Species and Antimicrobial Agent Tested	Range	Susceptible	Resistant
NDM-producing (n = 82)			
Ciprofloxacin	>1	…	100
Levofloxacin	>8	…	100
Amikacin	<2 to >32	6.1	93.9
Gentamicin	<1 to >16	8.5	91.5
Meropenem	≤0.125 to 64	6.1	93.9
Ertapenem	1 to >2	…	100
TMP-SMX	≤2/38 to >8/152	2.4	97.6
Tigecycline	≤0.25 to >4	84.1	15.9
Colistin	≤0.5 to >8	90.2	9.8
Fosfomycin	4 to 64	72	28
Aztreonam	<2 to >32	7.3	92.7
CAZ-AVI	>32	…	100
VIM-producing (n = 20)			
Ciprofloxacin	>1	…	100
Levofloxacin	>8	…	100
Amikacin	<2 to >32	5	95
Gentamicin	<2 to >16	20	80
Meropenem	2 to >64	25	75
Ertapenem	1 to >2	…	100
TMP-SMX	>4/76	…	100
Tigecycline	<0.5 to 6	50	50
Colistin	≤0.5 to >8	80	20
Fosfomycin	4 to 64	80	20
Aztreonam	<2 to >32	50	50
CAZ-AVI	>32	…	100

Table 3. Clinical Characteristics and Outcomes of Patients With Bloodstream Infection Due to Metallo-β-Lactamase–Producing Enterobacterales, by Treatment Regimen

Characteristic	Overall (N = 102)	CAZ-AVI + ATM (n = 52)	OAAs (n = 50)	*P* Value
Age, y, median (IQR)	70 (55–78)	69 (49.75–77)	70.5 (57.5–78)	.247
Male sex	69 (67.6)	36 (69.2)	33 (66)	.727
Ward of hospitalization				
Medical ward	49 (48)	21 (40.4)	28 (56)	.115
ICU ward	35 (34.3)	26 (50)	9 (18)	**.001**
Surgery	18 (17.6)	5 (9.6)	13 (26)	**.030**
Comorbidities				
Cardiovascular disease	41 (40.2)	22 (42.3)	19 (38)	.657
Solid cancer	35 (34.3)	16 (30.8)	19 (38)	.442
COPD	20 (19.6)	6 (11.5)	14 (28)	**.036**
Diabetes	34 (33.3)	20 (38.5)	14 (28)	.263
Chronic renal disease	15 (14.7)	8 (15.4)	7 (14)	.844
Chronic liver failure	10 (9.8)	3 (5.8)	7 (14)	.162
Solid organ transplantation	8 (7.8)	2 (3.8)	6 (12)	.126
Charlson comorbidity index, median (IQR)	4 (2–6.25)	4 (1–6)	4.5 (2–7)	.339
Immunosuppressive therapy, previous 30 d	35 (34.3)	10 (19.2)	25 (50)	**.001**
Source of infection				
Unknown	14 (13.7)	5 (9.6)	9 (18)	.219
Urinary tract	33 (32.4)	13 (25)	20 (40)	.105
Intravascular device	27 (26.5)	17 (32.7)	10 (20)	.146
Skin and soft tissue	12 (11.8)	9 (17.3)	3 (6)	.076
Respiratory tract	9 (8.8)	6 (11.5)	3 (6)	.324
Intra-abdominal	7 (6.9)	2 (3.8)	5 (10)	.219
Source control	58 (56.9)	34 (65.4)	24 (48)	.076
SOFA score, median (IQR)	4 (2–7)	4 (2–6)	5 (2–7.5)	.383
Septic shock	27 (26.5)	13 (25)	14 (28)	.731
Mechanical ventilation	31 (30.4)	17 (32.7)	14 (28)	.607
Time to in vitro active therapy ≤ 48 h	71 (69.6)	40 (76.9)	31 (62)	.101
Drug-induced AKI	11 (10.8)	1 (1.9)	10 (20)	**.003**
Duration of antibiotic therapy, d, median (IQR)	10 (7–14)	11 (8–14)	9 (5.75–12.5)	.081
Primary outcome				
30-d mortality	32 (31.4)	10 (19.2)	22 (44)	**.007**
Secondary outcome measures				
Clinical failure at day 14	39 (38.2)	13 (25)	26 (52)	**.005**
LOS after BSI[a], median (IQR)	16.5 (10–31.5)	14 (10–20.25)	23 (9.5–42.75)	.135

Table 2. Targeted Antibiotic Regimens Administered in 102 Bloodstream Infections Due to Metallo-β-Lactamase–Producing Enterobacterales

Antibiotic Regimen	No. (%) (N = 102)	Mortality, No. (%)
CAZ-AVI + ATM[a]	52 (51)	10/52 (19.2)
OAAs		
Colistin-containing regimens	27 (26.5)	16/27 (59.3)
Colistin + fosfomycin + tigecycline	7	6/7
Colistin + fosfomycin	7	5/7
Colistin + meropenem	5	3/5
Colistin + ATM ± piperacillin-tazobactam	4	1/4
Colistin + gentamicin	1	0/1
Colistin + cotrimoxazole	1	0/1
Colistin alone	2	1/2
Regimens not containing colistin	23 (22.5)	6/23 (26.1)
Tigecycline + aminoglycosides	8	2/8
Fosfomycin + aminoglycosides	5	0/5
Tigecycline + fosfomycin	2	2/2
Tigecycline + meropenem	1	0/1
ATM + aminoglycosides	4	1/4
ATM + fosfomycin	1	0/1
ATM alone	2	1/2

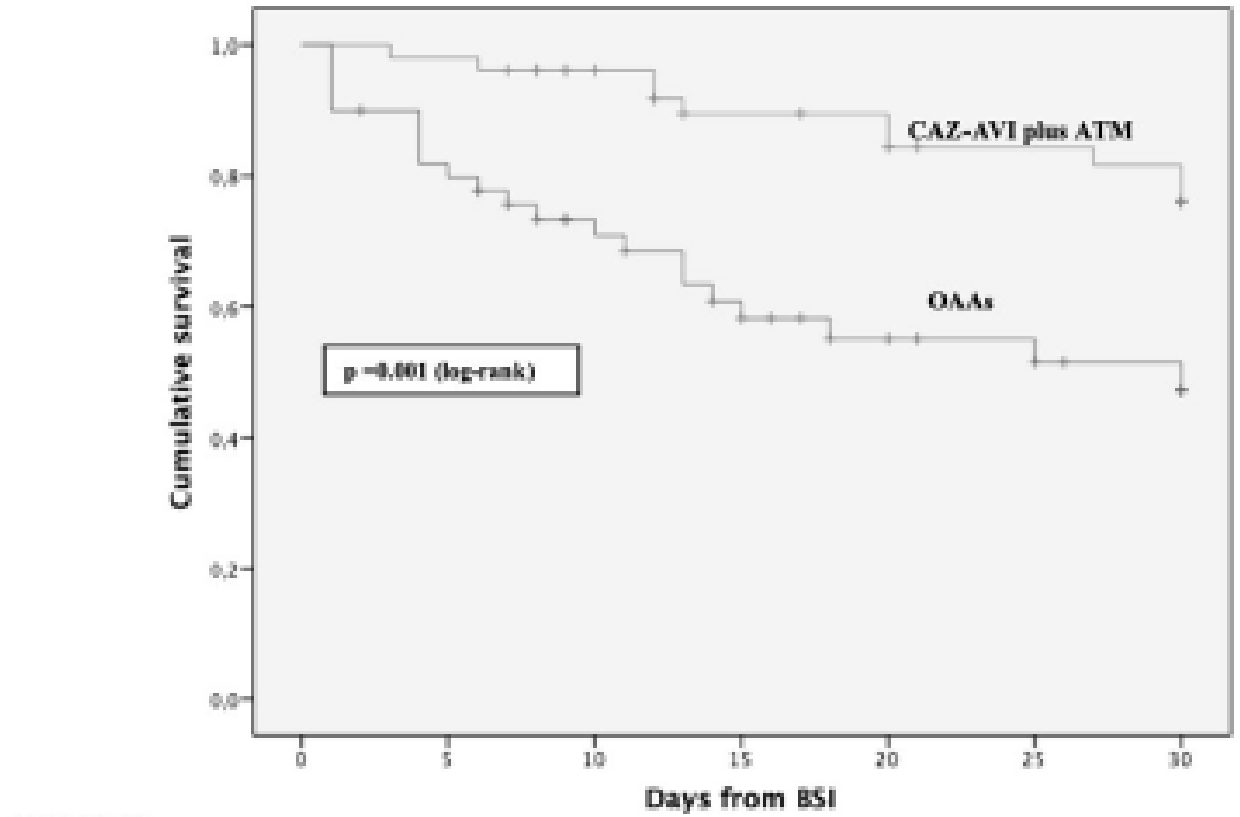
Abbreviations: ATM, aztreonam; CAZ-AVI, ceftazidime-avibactam; OAAs, other active antibiotics.

[a]In vitro activity is supported by in vitro synergistic tests.

Table 4. Cox Regression Analysis of Factors Independently Associated With 30-Day Mortality

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.



Number at risk

CAZ-AVI *plus* ATM	52	51	50	47	45	45	42
OAAs	50	40	36	31	30	29	28

Figure 1. Kaplan-Meier survival curves according to treatment regimen (ceftazidime-avibactam plus aztreonam vs other active antibiotics). Abbreviations:

Diskussion

- Mortalität mit Ceftazidim/Avibactam und Aztreonam reduziert
- Resultate bestärken Synergismuseffekt
- Colistin mit Morbidität und Mortalität vergesellschaftet
- Optimale PK/PD für Avibactam in Kombination mit Ceftazidim und Aztreonam ist noch nicht bekannt

Limitationen

- Nicht-randomisierte, observationelle Studie
- Geringe Patientenzahlen
- Möglicher «prescription bias»
- Keine Pharmakokinetik/-dynamik Untersuchung erfolgt