Journal Club 06.01.2020

J Antimicrob Chemother
doi:10.1093/jac/dkz437

Journal of Antimicrobial Chemotherapy

β-Lactam pharmacodynamics in Gram-negative bloodstream infections in the critically ill

Gloria Wong[1,2]*, Fabio Taccone[3], Paola Villois[3], Marc H. Scheetz[4–6], Nathaniel J. Rhodes[4–6], Scott Briscoe[7], Brett McWhinney[7], Maria Nunez-Nunez[8], Jacobus Ungerer[7,9], Jeffrey Lipman[1,2,10] and Jason A. Roberts[1,2,10,11]

[1]UQ Centre for Clinical Research, The University of Queensland, Brisbane, Queensland, Australia; [2]Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia; [3]Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium; [4]Department of Pharmacy, Northwestern Memorial Hospital, Chicago, IL, USA; [5]Department of Pharmacy Practice and Pharmacometrics Center of Excellence, Midwestern University, Chicago College of Pharmacy, Downers Grove, IL, USA; [6]Department of Pharmacology, College of Graduate Studies, Midwestern University, Chicago College of Pharmacy, Downers Grove, IL, USA; [7]Chemical Pathology, Pathology Queensland, Brisbane, Queensland, Australia; [8]Department of Pharmacy and Department of Infectious Diseases, University Hospital San Cecilio, Granada, Spain; [9]Faculty of Medicine, University of Queensland, Brisbane, Queensland, Australia; [10]Division of Anaesthesiology Critical Care Emergency and Pain Medicine, Nîmes University Hospital, University of Montpellier, Nîmes, France; [11]Centre for Translational Anti-infective Pharmacodynamics, School of Pharmacy, The University of Queensland, Brisbane, Queensland, Australia

*Corresponding author. E-mail: gloria.wong@alumni.utoronto.ca

Received 22 May 2019; returned 5 July 2019; revised 17 September 2019; accepted 25 September 2019

Hintergrund

- Bloodstream Infections (BSI) assoziiert mit hoher Mortalität in kritisch kranken Patienten

  Schwab F et al, ICU mortality following ICU acquired BSI, PLOS One 2018

- Effizienz von B-laktam Antibiotika korreliert mit der Zeit der Antibiotikakonzentration über der MIC
  - In vitro- und Tierstudien; abhängig von der B-Laktam Subklasse ein PK/PD Index von mind. 30-60% fT>MIC für bakteriziden Effekt notwendig ist
  - Einige Reports beschreiben, dass Talkonzentrationen gewisser Antibiotika bis 5-6 x > MIC mit einem besseren Outcome assoziert sind

Ziel der Studie

- Im Kontext von gramnegativen BSI ist unklar welcher PK/PD Index für B-Laktame optimal in kritisch kranken Patienten ist
- Ziel: PD der B-Laktame in kritisch kranken Patienten mit gramnegativer BSI zu untersuchen und zu definieren welcher PK/PD Index > MIC mit einem besseren Outcome assoziiert ist

Patientenselektion

- Retrospektive Studie
- 2 Datensets (prospektive datasets)
  - TDM database from the ICUs within Erasme Hospital in Belgium
  - TDM database from the Royal Brisbane and Women‘s hospital
- Einschlusskriterien
  - Dokumentierte BSI welche durch 1 Pathogen verursacht
  - Aufenthalt auf ICU
  - Alter > 18
- Ausschlusskriterien
  - RRT
  - Polymikrobielle BSI
  - CF- und Verbrennungspatienten (belgische Database)

Endpunkt

Table 1. Definitions of clinical outcomes

Clinical outcome	
Positive clinical outcome	Completion of treatment course without change or addition of antibiotic therapy, and with no additional antibiotics commenced within 48 h of cessation. De-escalation to a narrower-spectrum antibiotic was permitted.
Negative clinical outcome	Any clinical outcome other than positive clinical outcome.

Resultate

- 98 Patienten in Studie eingeschlossen

Table 2. Demographics and clinical characteristics of patients studied

Characteristic	Overall ($N = 98$)	Positive outcome ($N = 78$)[a]	Negative outcome ($N = 20$)[a]
Age (years), mean ± SD	59 ± 16	59 ± 16	57 ± 17
Male sex, *n* (%)	67 (68.4)	53 (67.9)	14 (70.0)
BMI (m^2/kg), mean ± SD[b]	26.7 ± 5.5	26.8 ± 5.8	26.4 ± 4.3
APACHE II score, mean ± SD	21 ± 7	21 ± 7	20 ± 8
Measured CL_{CR} (mL/min), median (IQR)[c]	77.5 (4–402)	92.0 (49.3–120.5)	103 (50.3–132.4)
Augmented renal clearance, *n* (%)[d]	22 (22.4)	16 (20.5)	6 (30.0)

[a]No significant difference between groups ($P > 0.5$).
[b]Data only available for 79 patients.
[c]Based on 24 h urinary CL_{CR}.
[d]Defined as CL_{CR} >130 mL/min.

Pathogene und MICs

Table 3. Microbiological pathogens of BSI ($N = 98$) and MICs of corresponding β-lactams

		MIC (mg/L), median (range)					
Pathogen	*n* (%)	TZP	MEM	CAZ	CRO	ATM	FEP
Acinetobacter baumannii	1 (1.0)	64	—	—	—	—	—
Citrobacter koseri	2 (2.0)	1.5	0.012	—	—	—	—
Enterobacter aerogenes	4 (4.1)	—	1.125 (0.25–6)	—	—	—	—
Enterobacter cloacae	9 (9.2)	3 (2–8)	0.157 (0.016–0.25)	—	—	—	—
E. coli	28 (28.6)	3 (1.5–8)	0.023 (0.016–0.25)	0.19 (0.125–0.25)	1.5 (1–2)	—	—
Klebsiella oxytoca	5 (5.1)	8	0.032 (0.032–0.064)	0.064	—	—	—
K. pneumoniae	13 (13.3)	4 (1.5–8)	0.023 (0.016–48)	—	—	—	—
Klebsiella spp.	2 (2.0)	4	0.25	—	—	—	—
Morganella morganii	3 (3.1)	1.5	0.0785 (0.032–0.125)	—	—	—	—
P. aeruginosa	19 (19.4)	8 (2–256)	4.25 (0.012–48)	5.5 (1.5–32)	—	18 (12–24)	132 (8–256)
Proteus mirabilis	9 (9.2)	0.75 (0.25–1)	0.064 (0.032–0.125)	—	—	—	—
Proteus vulgaris	1 (1.0)	—	0.064	—	—	—	—
Serratia liquefaciens	1 (1.0)	4	—	—	—	—	—
Serratia marcescens	1 (1.0)	—	0.064	—	—	—	—

TZP, piperacillin/tazobactam; MEM, meropenem; CAZ, ceftazidime; CRO, ceftriaxone; ATM, aztreonam; FEP, cefepime.

PK/PD Data, Clinical Outcome

Table 4. PK/PD index and clinical outcome for studied β-lactam antibiotics in critically ill patients treated for Gram-negative BSI

Antibiotic, *n* (%)	Daily dose (g), median (IQR)	fC_{min}/MIC ratio, *n* (%)			Positive clinical outcome, *n* (%)
		<1	1–5	>5	
Aztreonam, 2 (2.0)	7.0 (6.0–5.0)	—	—	2 (100.0)	2 (100.0)
Ceftazidime, 10 (10.2)	6.0 (4.0–12.0)	—	3 (30.0)	7 (70.0)	7 (70.0)
Cefepime, 2 (2.0)	6.0 (6.0–6.0)	2 (100.0)	—	—	0 (0.0)
Ceftriaxone, 2 (2.0)	3.0 (2.0–4.0)	—	—	2 (100.0)	2 (100.0)
Meropenem, 46 (46.9)	3.0 (2.0–6.0)	3 (6.5)	4 (8.7)	39 (84.8)	42 (91.3)
Piperacillin/tazobactam, 36 (36.7)	16.0 (8.0–16.0)	7 (19.4)	9 (25.0)	20 (55.6)	25 (69.4)
Overall (*N*=98)		12 (12.2)	16 (16.3)	70 (71.4)	78 (79.6)

PK/PD outcome was measured in terms of the ratio of unbound trough (fC_{min}) to MIC for the pathogen of corresponding β-lactams.

CART Analyse

Node 0 (all patients)		
	%	*n*
Negative outcome	20.4	20
Positive outcome	79.6	78
Total	100	98

fC_{min}/MIC

Node 1 (fC_{min}/MIC ≤1.3)		
	%	*n*
Negative outcome	50.0	7
Positive outcome	50.0	7
Total	14.3	14

Node 2 (fC_{min}/MIC >1.3)		
	%	*n*
Negative outcome	15.5	13
Positive outcome	84.5	71
Total	85.7	84

Figure 1. CART analysis for association of the fC_{min}/MIC with positive clinical outcome in all studied patients ($N=98$; $P<0.05$). Positive outcome was associated with an fC_{min}/MIC ratio of >1.3.

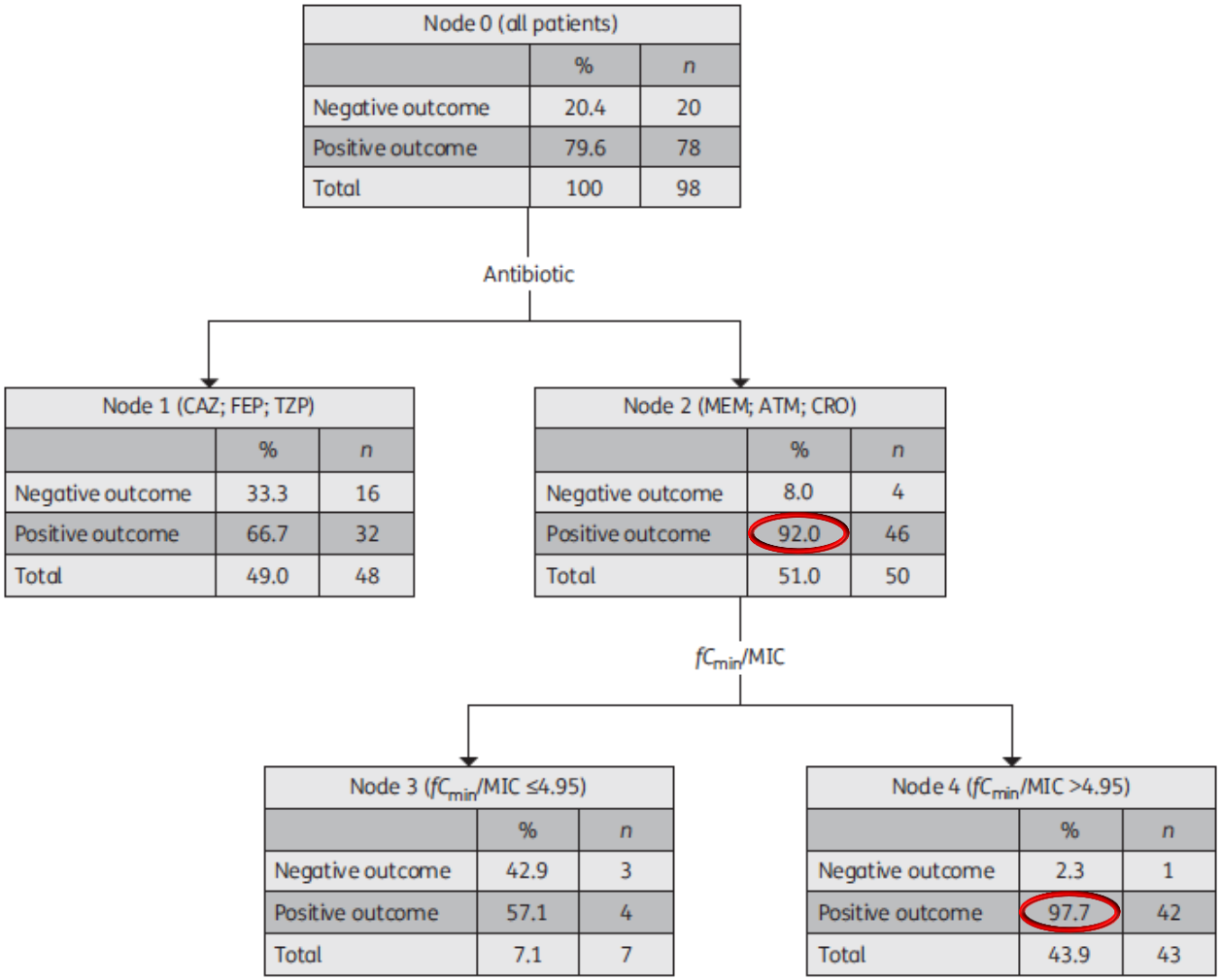

Figure 2. CART analysis for association of the fC_{min}/MIC ratio with positive clinical outcome in patients, according to β-lactam antibiotics received. Positive dinical outcome is associated with a significantly higher fC_{min}/MIC ratio of >4.95 in patients who received meropenem, aztreonam or ceftriaxone ($N = 50$; $P < 0.05$). CAZ, ceftazidime; FEP, cefepime; TZP, piperacillin/tazobactam; MEM, meropenem; ATM, aztreonam; CRO, ceftriaxone.

Schwachstellen der Studie

- Kleine Fallzahl, wobei gemäss Autoren bisher die grösste Patientenzahl mit in-vivo Daten analysiert
- Signifikanz nur wenn mehrere Antibiotika zusammen analysiert (Meropenem/Aztreonam/Ceftriaxon alleine keine Signifikanz)
- Einige freie Konzentrationen errechnet und nicht gemessen
- Mikrobiologisches Outcome / Clearance der Bakteriämie nicht untersucht
- Keine Aussage über Fokus oder weitere Infektionsherde
- RRT als Ausschlusskriterium
- ...

Danke für eure Aufmerksamkeit!

Diskussion