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Podporujeme výskumné aktivity na Slovensku/Projekt je spolufinancovaný zo zdrojov EÚ

NOVÉ MOŽNOSTI LIEČBY U PACIENTOV S POPÁLENINAMI

PAVOL JARČUŠKA

Kongres Slovenskej spoločnosti pre liečbu rán, Demänovská dolina 10.11.2018

Nové možnosti liečby u pacientov s popáleninami

Pavol Jarčuška

Table 3 Ambler classification of β-lactamases[41]

Ambler classification	Representative examples
A	CTX-M, SHV, TEM, KPC, GES, SME
B	PER, VEB, IMP, NDM, VIM
C	AmpC, FOX, CMY, LAT, ACC, DHA
D	OXA enzymes (OXA-1, OXA-48, OXA-10)

	Ceftolozane-tazobactam	Ceftazidime-avibactam
FDA indications	Complicated intra-abdominal infections (cIAI) (with metronidazole), complicated UTI (including pyelonephritis)	Complicated intra-abdominal infections (cIAI) (with metronidazole), complicated UTI (including pyelonephritis)
Gram negative activity**	*E. coli* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Proteus mirabilis* *Pseudomonas aeruginosa* *Enterobacter cloacae*	*E. coli* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Proteus mirabilis* *Pseudomonas aeruginosa* *Enterobacter cloacae* *Enterobacter aerogenes* *Citrobacter koseri* *Citrobacter freundii*
Gram positive activity**	*Streptococcus anginosus* *Streptococcus constellatus* *Streptococcus salivarius*	NA
Anaerobic coverage**	*Bacteroides fragilis*	NA
Beta lactamase activity		
Class A (TEM, SHV, CTX-M, KPC, GES)	Variable activity (not on carbapenemases)	Active including carbapenemases (KPC)
Class B (NDM, VIM, IMP)	No activity	No activity
Class C (AmpC)	Variable activity	Yes
Class D (OXA)	Active against OXA-type ESBL but not OXA-type carbapenemases	Variable activity

Organism (#)	CTZ-AVM MIC_{50}	CTZ-AVM MIC_{90}	MIC range	# (%) Susceptible	CFZ-TZM MIC_{50}	CFZ-TZM MIC_{90}	MIC range	# (%) Susceptibl
Pseudomonas aeruginosa (31)	1.5	6	0.5-16	29 (94)	0.75	3	0.25-≥256	30 (97)
PTZ R (11)	3	8	1-12	10(91)	1.5	4	0.38-4	11 (100)
Ceftazidime R (8)	6	12	1.5-12	7 (88)	1.5	2	0.75-4	8 (100)
Cefepime R (6)	6	12	2-12	5 (83)	1.5	4	0.75-4	6 (100)
Gentamicin R (5)	3	16	1.5-16	4 (80)	0.75	≥256	0.75-≥256	4 (80)
Ciprofloxacin R (8)	4	16	1.5-16	7 (88)	1	≥256	0.75-≥256	7 (88)
Meropenem R (16)	2	12	0.75-16	14 (88)	0.75	4	0.25-≥256	15 (94)
MDR (9)	6	16	1.5-16	7 (78)	1.5	≥256	0.75-≥256	8 (89)
XDR (5)	6	16	2-16	4 (80)	1.5	≥256	0.75-≥256	4 (80)

β-LACTAMASE	AVYCAZ
Serine carbapenemases (KPCs)	✓
ESBLs: TEM, SHV, CTX-M families	✓
Cephalosporinases (AmpCs)	✓
Some oxacillinases (OXA)	✓

	Favorable microbiological response rate					
	CAZ-AVI (N=144)			BAT (N=137)		
Patient subgroup	n	m (%)[a]	95% CI[b]	n	m (%)[a]	95% CI[b]
All patients	144	118 (81.9)	75.1, 87.6	137	88 (64.2)	56.0, 71.9
Patients with any MIC-screened pathogen	143	118 (82.5)	75.7, 88.1	135	86 (63.7)	55.4, 71.5
Patients with only MIC-screen negative pathogens	1	1 (100)	14.7, 100	0	0	NA
Patients with any MIC-screen positive pathogens	142	117 (82.4)	75.5, 88.0	135	86 (63.7)	55.4, 71.5
Patients without any Category I β-lactamase gene identified	1	0 (0)	0.0, 85.3	1	0 (0)	0.0, 85.3
Patients with any Category I β-lactamase gene identified	139	116 (83.5)	76.6, 88.9	134	86 (64.2)	55.8, 71.9
Patients with only Category I β-lactamase gene identified	16	13 (81.3)	57.9, 94.4	13	9 (69.2)	42.3, 88.6

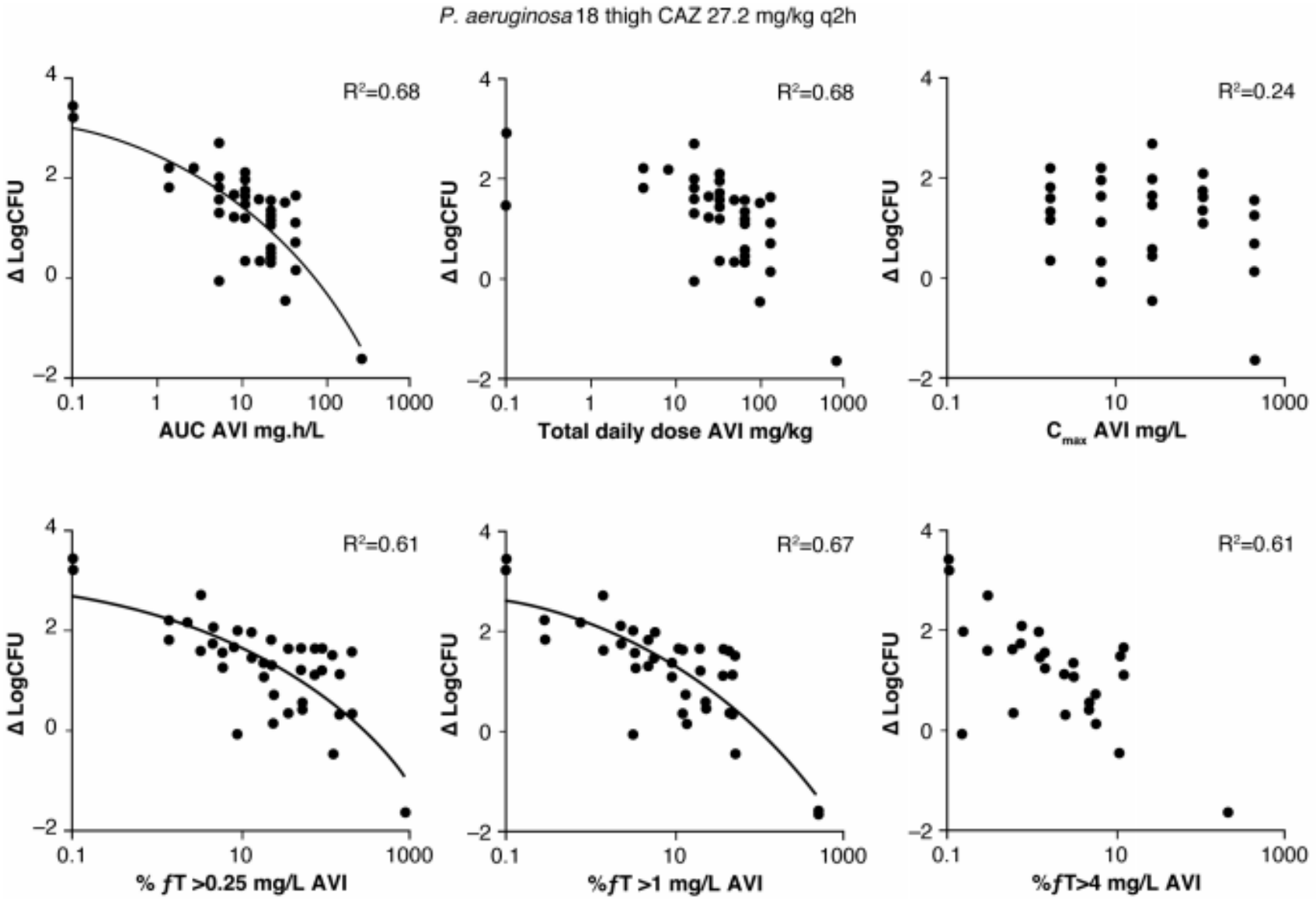


FIG 2 Dose fractionation study of avibactam in combination with ceftazidime against a ceftazidime-resistant *P. aeruginosa* strain in the neutropenic mouse thigh infection model.

AVI, avibactam; CAZ, ceftazidime; Δ*log*CFU, change in $\log_{10}$ CFU compared to the initial inoculum.

Figure from Berkhout et al (44). Reproduced with permission from American Society for Microbiology.

Ceftazidime[a]	
C_{max} (mg/l)	79.8 (41.8)
t_{max} (h)[c]	2.0 (1.9–2.6)
AUC_{0-t} (h·mg/l)	229.2 (30.9)
$AUC_{0-infinity}$ (h·mg/l)	230.6 (30.7)
$t_{1/2}$ (h)[c]	1.7 (0.9–2.8)
V_{ss} (l)	22.2 (42.0)
CL (l/h)	8.7 (45.5)
CL/W (l/kg/h)	0.169 (37.9)
Avibactam[a]	
C_{max} (mg/l)	15.1 (52.4)
t_{max} (h)	2.0 (1.9–2.6)
AUC_{0-t} (h·mg/l)	36.3 (33.7)
$AUC_{0-infinity}$ (h·mg/l)	36.4 (33.6)

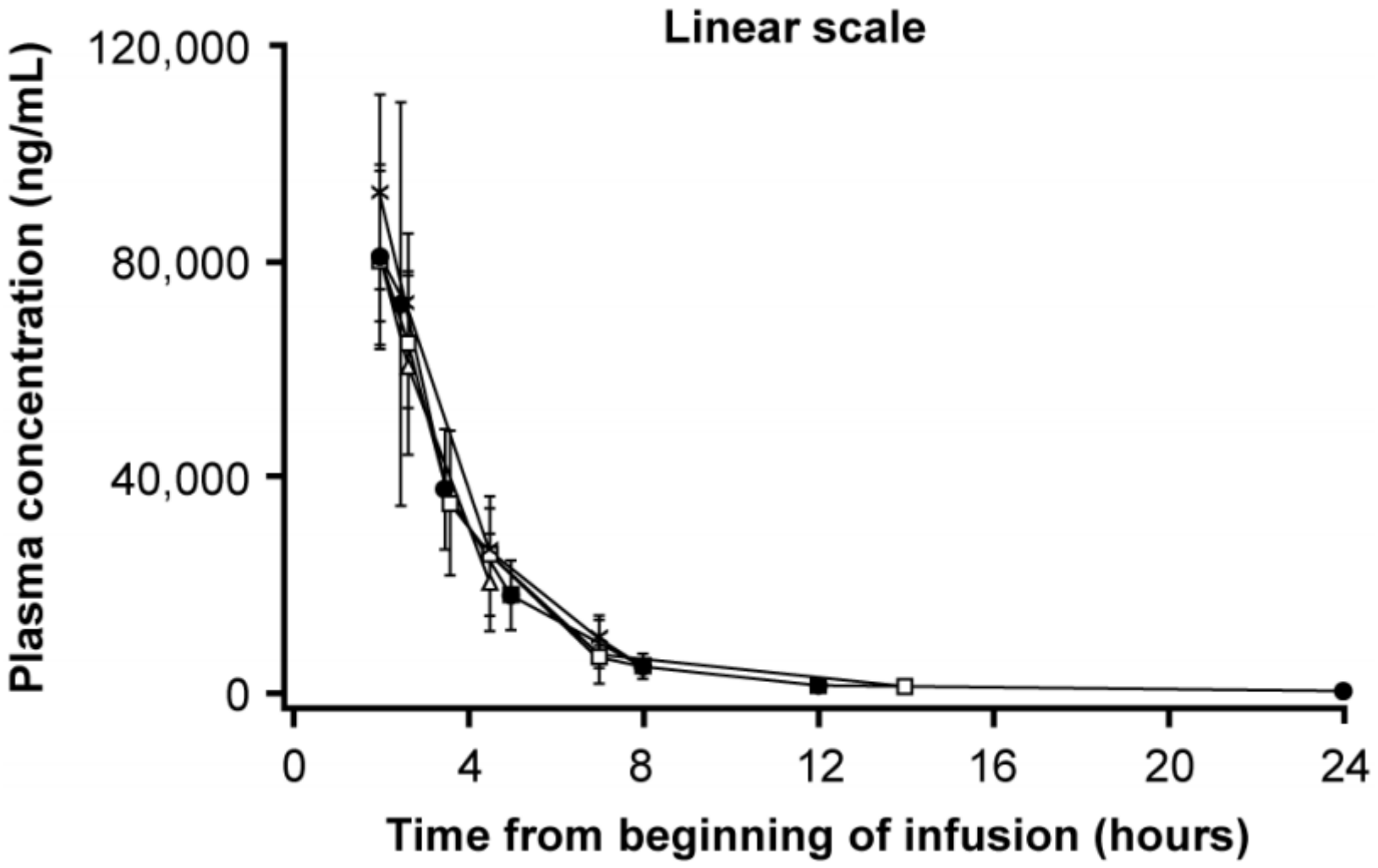
	Cohort 1 (≥12 yr to <18 yr) (*n* = 8)	Cohort 2 (≥6 yr to <12 yr) (*n* = 8)	Cohort 3 (≥2 yr to <6 yr) (*n* = 8)	Cohort 4 (≥3 m to <2 yr) (*n* = 8)
Ceftazidime[a]				
C_{max} (mg/l)	79.8 (41.8)	81.3 (17.8)	80.1 (14.7)[b]	91.7 (19.6)[b]
t_{max} (h)[c]	2.0 (1.9–2.6)	2.1 (1.9–2.4)	–	–
AUC_{0-t} (h·mg/l)	229.2 (30.9)	217.8 (18.4)	–	–
$AUC_{0-infinity}$ (h·mg/l)	230.6 (30.7)	221.2 (17.4)	–	–
$t_{1/2}$ (h)[c]	1.7 (0.9–2.8)	1.6 (0.9–1.8)	–	–
V_{ss} (l)	22.2 (42.0)	13.0 (17.8)	–	–
CL (l/h)	8.7 (45.5)	5.6 (16.0)	–	–
CL/W (l/kg/h)	0.169 (37.9)	0.226 (20.0)	–	–
Avibactam[a]				
C_{max} (mg/l)	15.1 (52.4)	14.1 (23.0)	13.7 (22.4)[b]	16.3 (22.6)[b]
t_{max} (h)	2.0 (1.9–2.6)	2.1 (1.9–2.4)	–	–
AUC_{0-t} (h·mg/l)	36.3 (33.7)	34.4 (23.4)	–	–
$AUC_{0-infinity}$ (h·mg/l)	36.4 (33.6)	34.8 (22.6)	–	–

TABLE 4 Summary of ceftazidime and avibactam observed and population pharmacokinetic model-predicted exposures in pediatric patients (pharmacokinetic population)

$AUC_{0\text{-infinity}}$ (h·mg/l)	Cohort 1[a] (≥12 to <18 yr) (*n* = 8)	Cohort 2[a] (≥6 to <12 yr) (*n* = 8)	Cohort 3[b] (≥2 to <6 yr) (*n* = 8)	Cohort 4[b] (≥3 m to <2 yr) (*n* = 8)	Adult reference population[c] (*n* = 16)
	Observed		Predicted		
Ceftazidime					
	230.6 (30.7)	221.2 (17.4)	255.32 (43.95)	286.27 (37.13)	289.0 (15.4)[d]
Avibactam					
	36.4 (33.6)	34.8 (22.6)	43.25 (12.14)	48.99 (10.64)	42.1 (16.0)[e]

Table 20: Comparison of ceftazidime and avibactam exposure and target attainment in phase 3 patients stratified across different obesity classes

Covariate Category: Obesity	n	CAZ $C_{max,ss}$ (mg/L)	CAZ $AUC_{ss,0-24}$ (mg.h/L)	AVI $C_{max,ss}$ (mg/L)	AVI $AUC_{ss,0-24}$ (mg.h/L)	Target attainment at MIC of 8 mg/L (%)
Normal	1084	77.4 (104.0)	876 (110.3)	12.9 (154.1)	134 (154.4)	99.1 (98.5, 99.6)
Obesity I	182	76.6 (100.2)	961 (123.8)	13.1 (148.0)	150 (163.9)	98.9 (97.4, 100.0)
Obesity II	62	68.7 (97.2)	899 (126.7)	11.4 (137.9)	137 (153.4)	98.4 (95.3, 100.0)
Obesity III	23	63.4 (77.0)	795 (101.5)	9.73 (97.1)	115 (113.6)	100.0 (NA)


Linear scale
Plasma concentration (ng/mL)
120,000
80,000
40,000
0
0
4
8
12
16
20
24
Time from beginning of infusion (hours)

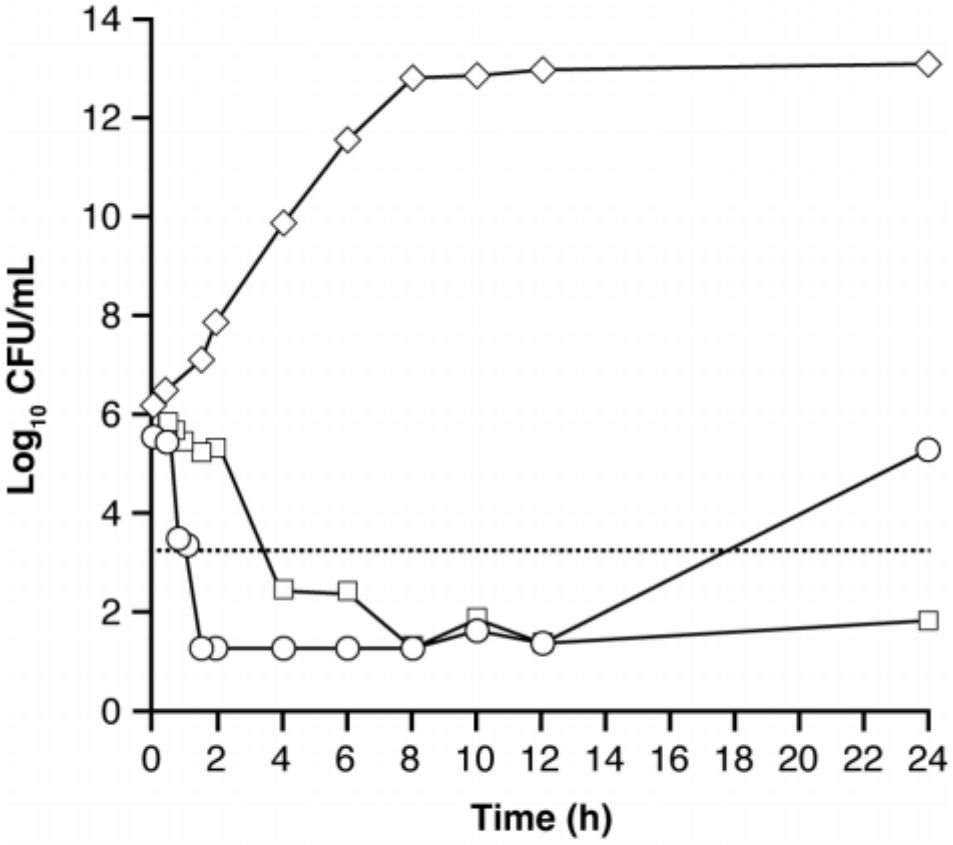


FIG 1 Responses of ceftazidime-resistant *E. cloacae* to continuous infusion of ceftazidime combined with two different concentration-time profiles of avibactam in the hollow fiber model.

4.1 Therapeutic indications

Zavicefta is indicated for the treatment of the following infections in adults (see sections 4.4 and 5.1):

- Complicated intra-abdominal infection (cIAI)
- Complicated urinary tract infection (cUTI), including pyelonephritis
- Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP)

Zavicefta is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options (see sections 4.2, 4.4 and 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

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Ceftazidime-Avibactam as Salvage Therapy for Infections Caused by Carbapenem-Resistant Organisms

Elizabeth Temkin,[a] Julian Torre-Cisneros,[i,j] Bojana Beovic,[b] Natividad Benito,[c,] Maddalena Giannella,[e] Raúl Gilarranz,[f] Cameron Jeremiah,[g] Belén Loeches,[h] Isabel Machuca,[i,j] María José Jiménez-Martín,[k] José Antonio Martínez,[l] Marta Mora-Rillo,[h] Enrique Navas,[m] Michael Osthoff,[n] Juan Carlos Pozo,[o] Juan Carlos Ramos Ramos,[h] Marina Rodriguez,[o] Miguel Sánchez-García,[k] Pierluigi Viale,[p] Michel Wolff,[q,r] Yehuda Carmeli[a,s]

TABLE 4 Outcomes of patients with carbapenem-resistant infections treated with compassionate-use CAZ-AVI, by infection site

Infection site[a]	Total no. of cases	No. (%) of cases with:			Patients with:				Mortality among patients with microbiological cure	
		Bacteremia	Life-threatening infection	Documented microbiological cure	Clinical cure		In-hospital death			
					No. (%)	95% CI	No. (%)	95% CI	No. (%)	95% CI
All patients	38	26 (68.4)	23 (60.5)	24 (63.2)	26 (68.4)	51.3–82.5	15 (39.5)	24.0–56.6	5 (20.8)	7.1–42.2
Intra-abdominal	15	11 (73.3)	8 (53.3)	6 (40.0)	10 (66.7)	38.4–88.2	6 (40.0)	16.3–67.7	1 (16.7)	0.4–64.1
Pneumonia[b]	7	6 (85.7)	5 (71.4)	3 (42.9)	3 (42.9)	9.9–81.6	5 (71.4)	29.0–96.3	1 (33.3)	0.8–90.6
Skin and soft tissue	4	3 (75.0)	1 (25.0)	1 (25.0)	1 (25.0)	0.6–80.6	2 (50.0)	6.8–93.2	0 (0.0)	0.0–97.5
Urinary tract	3	2 (66.7)	1 (33.3)	2 (66.7)	2 (66.7)	9.4–99.2	2 (66.7)	9.4–99.2	1 (50)	1.3–98.7
Primary or catheter-associated bacteremia	7	7 (100)	7 (100)	7 (100.0)	7 (100)	59.0–100	1 (14.3)	0.4–57.9	1 (14.3)	0.4–57.9
Any bacteremia	26	26 (100)	20 (76.9)	18 (69.2)	18 (69.2)	48.2–85.7	11 (42.3)	23.4–63.1	4 (22.2)	6.4–47.6
Endocarditis	2	1 (50.0)	1 (50.0)	2 (100.0)	2 (100.0)	15.8–100	1 (50.0)	1.3–98.7	1 (50)	1.3–98.7
Osteomyelitis	3	0 (0.0)	0 (0.0)	2 (66.7)	2 (66.7)	9.4–99.2	1 (33.3)	0.8–90.6	0 (0.0)	0.0–84.2
Surgical site infection	2	1 (50.0)	2 (100)	1 (50.0)	1 (50.0)	1.3–98.7	1 (50.0)	1.3–98.7	0 (0.0)	0.0–97.5
Other[c]	3	1 (33.3)	2 (66.7)	3 (100)	2 (66.7)	9.4–99.2	1 (33.3)	0.8–90.6	1 (33.3)	0.8–90.6

[a]Patients may have multiple infection sites.

[b]Pneumonia cases included 6 cases of ventilator-associated pneumonia and 1 case of hospital-acquired pneumonia.

[c]Other infection types (1 patient each) were ventriculitis/subdural abscess, prosthetic joint infection, and mucositis.

TABLE 1 Antimicrobial susceptibility of isolates from patients with carbapenem-resistant infections treated with compassionate-use CAZ-AVI

Antibiotic	No. of isolates tested[a]	% Susceptible
Imipenem	36	2.8[b]
Meropenem	33	0.0
Ceftazidime	38	0.0
Colistin	34	41.2
Gentamicin	37	51.4
Amikacin	38	31.6
Tigecycline	32	62.5
Fosfomycin	29	55.2

[a]Sample included 34 *K. pneumoniae*, 1 *K. oxytoca*, 1 *E. coli*, and 2 *P. aeruginosa* isolates.

[b]Patient with OXA-48-producing *E. coli* who had failed imipenem treatment (MIC not reported).

HABP/VABP—REPROVE

AVYCAZ vs meropenem (N=870)
A phase 3, multinational, multicenter, double-blind, randomized, noninferiority trial studying AVYCAZ vs meropenem for the treatment of HABP/VABP[1]

See the REPROVE data

HABP/VABP, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia.

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cUTI—RECAPTURE

AVYCAZ vs doripenem (N=1020)
A phase 3, multinational, multicenter, double-blind, randomized noninferiority trial studying AVYCAZ vs doripenem for the treatment of cUTI, including acute pyelonephritis and complicated lower urinary tract infections[1]

cUTI, complicated urinary tract infections.

cUTI—REPRISE

AVYCAZ vs BAT (N=305)
A phase 3, multinational, randomized, open-label trial comparing AVYCAZ vs BAT for the treatment of cUTI due to ceftazidime-nonsusceptible Gram-negative pathogens. BAT options were meropenem, imipenem, doripenem, and colistin[1]

BAT, best available therapy.

cIAI—RECLAIM

AVYCAZ plus metronidazole vs meropenem (N=1058)
A phase 3, multinational, double-blind, noninferiority trial studying AVYCAZ plus metronidazole versus meropenem for the treatment of cIAI[1]

cIAI, complicated intra-abdominal infections.

HABP/VABP Trial—REPROVE

HABP/VABP Phase 3 trial vs meropenem[1]

STUDY DESIGN[1]

TYPE OF TRIAL	Phase 3, multinational, multicenter, double-blind, randomized, noninferiority trial
STUDY POPULATION	870 hospitalized adults with HABP/VABP; the ITT population included all randomized patients who received study drug. The micro-ITT population included all patients with at least one Gram-negative pathogen. The median age was 66 years and 74.1% were male. The median APACHE II score was 14. The majority of patients were from China (33.1%) and Eastern Europe (25.5%). There were no patients enrolled within the United States. Overall, 43.6% of patients were ventilated at enrollment, including 33.3% with VABP and 10.2% with ventilated HABP. Bacteremia at baseline was present in 4.8% of patients.
COMPARATIVE AGENTS	AVYCAZ® 2.5 g (ceftazidime 2 grams and avibactam 0.5 grams) IV every 8 hours Meropenem 1 gram intravenously every 8 hours

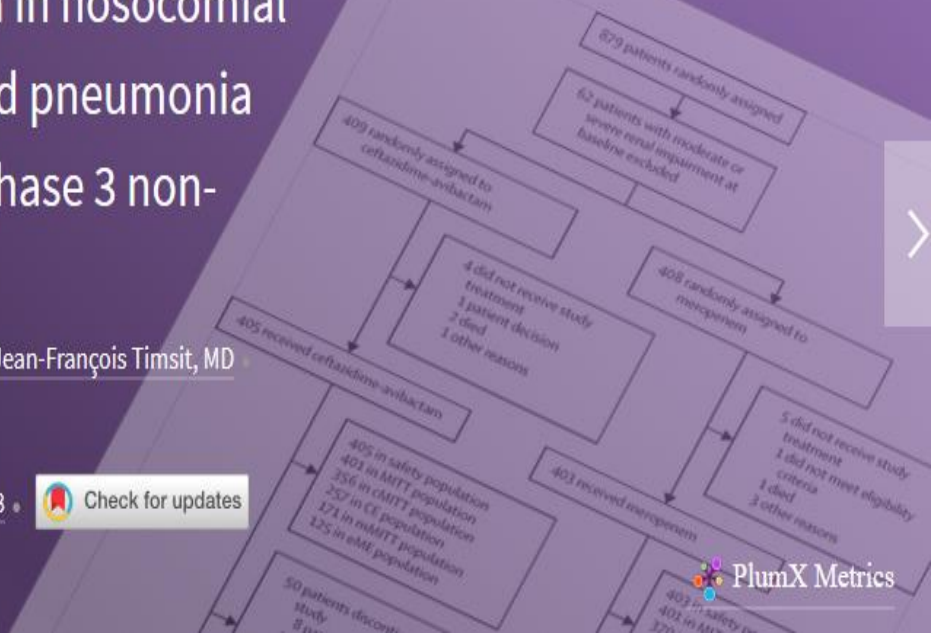
THE LANCET
Infectious Diseases

ARTICLES | VOLUME 18, ISSUE 3, P285-295, MARCH 01, 2018

Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial

Prof Antoni Torres, MD • Prof Nanshan Zhong, MD • Prof Jan Pachl, MD • Prof Jean-François Timsit, MD • Prof Marin Kollef, MD • Zhangjing Chen, MD • et al Show all authors

Published: December 15, 2017 • DOI: https://doi.org/10.1016/S1473-3099(17)30747-8 •

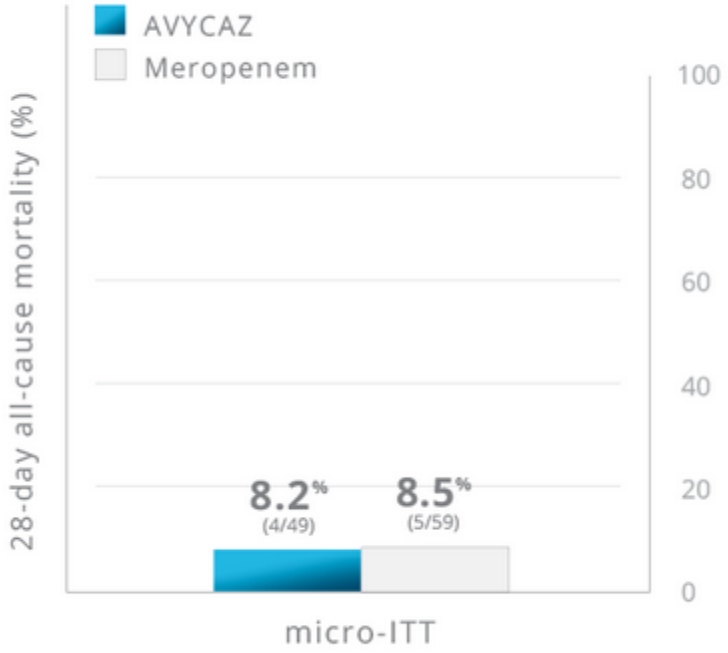


CEFTAZIDIME-NS SUBSET POPULATION: CLINICAL CURE RATES AT TOC (micro-ITT)[1]

NS, nonsusceptible.

micro-ITT, microbiological intent-to-treat.

CEFTAZIDIME-NS SUBSET POPULATION; 28-DAY ALL-CAUSE MORTALITY (micro-ITT)[1]



Clinical efficacy in cUTI involving ESBLs and AmpC[1]

- In a subset of Gram-negative pathogens from the Phase 3 cUTI trial, genotypic testing identified certain ESBL groups and AmpC in 21.7% (176/810) of patients in the mMITT population, all of which were expected to be inhibited by avibactam[1]:

TEM-1	SHV-12	CTX-M-15	CTX-M-27	OXA-48	AmpC

MICROBIOLOGICAL AND CLINICAL CURE RATES IN THIS SUBSET WERE SIMILAR TO THE OVERALL RESULTS[1]

ESBLs, extended-spectrum beta-lactamases.

mMITT, microbiologically modified intent-to-treat.

Clinical data by pathogen

MICROBIOLOGICAL CURE RATE BY BASELINE PATHOGEN AT TOC (mMITT)[1]

	AVYCAZ	Doripenem
Enterobacteriaceae	**78.3%** (299/382)	**70.6%** (281/398)
Escherichia coli	**78.4%** (229/292)	**71.9%** (220/306)
Klebsiella pneumoniae	**75.0%** (33/44)	**62.5%** (35/56)
Proteus mirabilis	**94.1%** (16/17)	**69.2%** (9/13)
Enterobacter cloacae	**54.5%** (6/11)	**69.2%** (9/13)
Pseudomonas aeruginosa	**66.7%** (12/18)	**75.0%** (15/20)

TOC, test of cure.

mMITT, microbiologically modified intent-to-treat.

Table 4
Safety evaluation up to late-follow-up visit (42–49 days after randomisation) (safety population) [*n* (%)][a].

	Ceftazidime/avibactam + metronidazole (*n* = 215)	Meropenem (*n* = 217)
AEs in ≥2% subjects in either treatment group by system organ class/preferred term[b] [*n* (%)]		
Nervous system disorders	7 (3.3)	6 (2.8)
Headache	3 (1.4)	5 (2.3)
Respiratory disorders	13 (6.0)	16 (7.4)
Productive cough	5 (2.3)	6 (2.8)
Cough	3 (1.4)	8 (3.7)
Gastrointestinal disorders	41 (19.1)	26 (12.0)
Nausea	18 (8.4)	4 (1.8)
Diarrhoea[c]	13 (6.0)	16 (7.4)
Constipation	5 (2.3)	3 (1.4)
Vomiting	5 (2.3)	4 (1.8)
General disorders	15 (7.0)	17 (7.8)
Pyrexia	9 (4.2)	13 (6.0)
Safety topics[d]		
Liver disorder	6 (2.8)	10 (4.6)
Diarrhoea	13 (6.0)	16 (7.4)
Hypersensitivity/anaphylaxis disorder	7 (3.3)	8 (3.7)
Haematological disorder	2 (0.9)	1 (0.5)
Renal disorder	1 (0.5)	1 (0.5)

AE, adverse event.

[a] Subjects with multiple AEs are counted once for each system organ class and/or preferred term.

[b] AEs are sorted by system organ class in international order and by preferred term in decreasing order of frequency in subjects treated with ceftazidime/avibactam + metronidazole.

[c] No cases of *Clostridium difficile* enterocolitis reported.

[d] Each safety topic represents the aggregate of a group of pre-identified relevant AE preferred terms based on those from previous a phase 2 study of ceftazidime/avibactam in complicated intra-abdominal infection.

Hindawi
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Volume 2018, Article ID 1854805, 5 pages
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Case Report

Prosthetic Joint Infection from Carbapenemase-Resistant *Klebsiella pneumoniae* Successfully Treated with Ceftazidime-Avibactam

A. Schimmenti,[1] E. Brunetti,[1,2] E. Seminari,[2] B. Mariani,[3] P. Cambieri,[3] and P. Orsolini[2,4]

[1]*Dipartimento di Scienze Clinico-Chirurgiche, Diagnostiche e Pediatriche, Unità di Malattie Infettive e Tropicali ed Epatologia, Università di Pavia, Pavia, Italy*
[2]*Unità di Malattie Infettive e Tropicali, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*
[3]*Microbiologia e Virologia, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*
[4]*Dipartimento di Medicina Interna e Terapia Medica, Università di Pavia, Pavia, Italy*

Correspondence should be addressed to P. Orsolini; orso@unipv.it

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Antibiotic	R/S	MIC mg/L
Amikacin	R	>16
Amoxicillin/cavulanate	R	>32/2
Ampicillin	R	>8
Cefepime	R	>8
Cefotaxime	R	>4
Ceftazidime	R	>8
Cefuroxime	R	>8
Ciprofloxacin	R	>1
Ertapenem	R	>1
Fosfomycin	S	≤16
Gentamicin	R	>256
Imipenem	R	>32
Levofloxacin	R	>2
Meropenem	R	>32
Piperacillin	R	>16
Piperacillin/tazobactam	R	>16/4
Tigecycline	S	0.25
Tobramycin	R	>4
Trimethoprim-sulfamethoxazole	S	≤1/19

Figure 3: Antibiotic susceptibility according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints of clinical *Klebsiella pneumonia* isolate. MIC: minimum inhibitory concentration; R: resistant; S: susceptible.

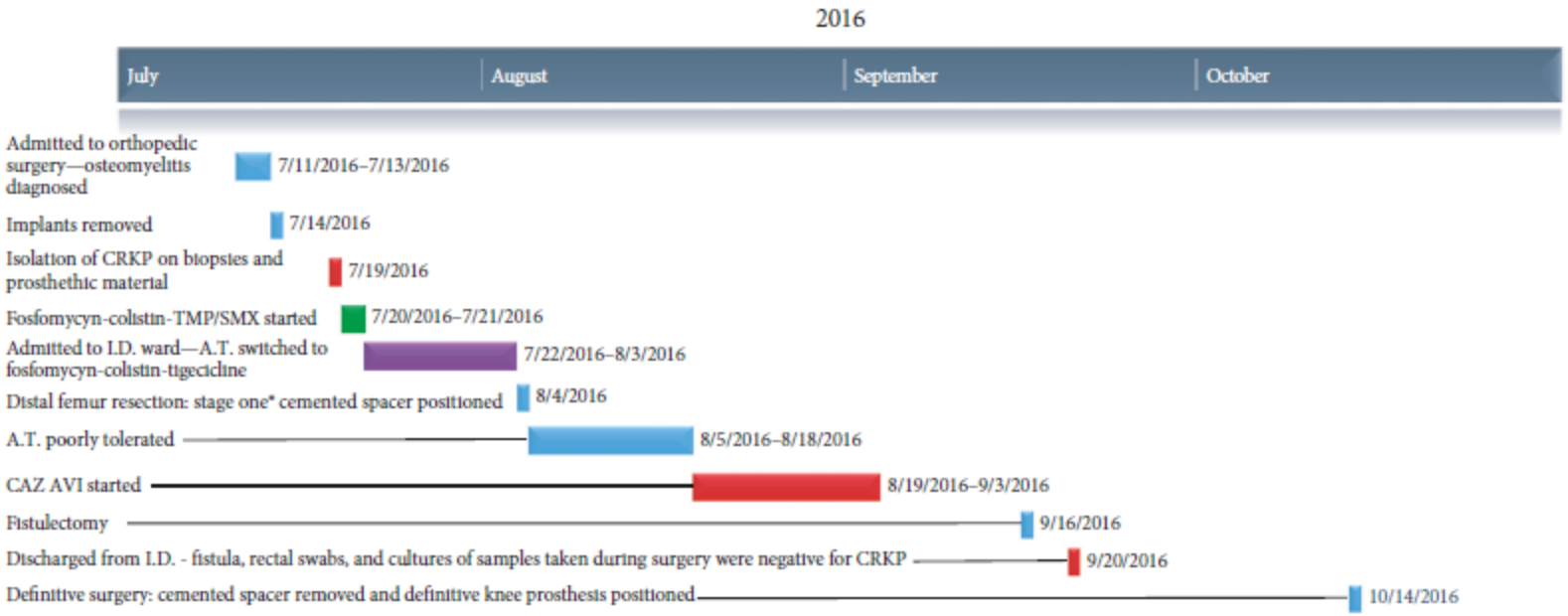

Figure 4: Timeline of antibiotic and surgical treatments.

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Phase I Study Assessing the Pharmacokinetic Profile, Safety, and Tolerability of a Single Dose of Ceftazidime-Avibactam in Hospitalized Pediatric Patients

John S. Bradley,[a] Jon Armstrong,[b] Antonio Arrieta,[c] Raafat Bishai,[d] Shampa Das,[b] Shirley Delair,[e] Timi Edeki,[f] William C. Holmes,[d] Jianguo Li,[g] Kathryn S. Moffett,[h] Deepa Mukundan,[i] Norma Perez,[j] José R. Romero,[k] David Speicher,[i] Janice E. Sullivan,[m] Diansong Zhou[g]

University of California, San Diego, California, USA[a]; AstraZeneca, Macclesfield, United Kingdom[b]; Children's Hospital of Orange County, Orange, California, USA[c]; AstraZeneca, Gaithersburg, Maryland, USA[d]; Children's Hospital & Medical Center, Omaha, Nebraska, USA[e]; AstraZeneca, Wilmington, Delaware, USA[f]; AstraZeneca, Waltham, Massachusetts, USA[g]; West Virginia University, Morgantown, West Virginia, USA[h]; University of Toledo, Toledo, Ohio, USA[i]; University of Texas Health Science Center, Houston, Texas, USA[j]; University of Arkansas for Medical Sciences and Arkansas Children's Hospital, Little Rock, Arkansas, USA[k]; University Hospitals Rainbow Babies and Children's Hospital, Cleveland, Ohio, USA[l]; University of Louisville and Kosair Children's Hospital, Louisville, Kentucky, USA[m]

This study aimed to investigate the pharmacokinetics (PK), safety, and tolerability of a single dose of ceftazidime-avibactam in pediatric patients. A phase I, multicenter, open-label PK study was conducted in pediatric patients hospitalized with an infection and receiving systemic antibiotic therapy. Patients were enrolled into four age cohorts (cohort 1, ≥12 to <18 years; cohort 2, ≥6 to <12 years; cohort 3, ≥2 to <6 years; cohort 4, ≥3 months to <2 years). Patients received a single 2-h intravenous infusion of ceftazidime-avibactam (cohort 1, 2,000 to 500 mg; cohort 2, 2,000 to 500 mg [≥40 kg] or 50 to 12.5 mg/kg [<40 kg]; cohorts 3 and 4, 50 to 12.5 mg/kg). Blood samples were collected to describe individual PK characteristics for ceftazidime and avibactam. Population PK modeling was used to describe characteristics of ceftazidime and avibactam PK across all age groups. Safety and tolerability were assessed. Thirty-two patients received study drug. Mean plasma concentration-time curves, geometric mean maximum concentration (C_{max}), and area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) were similar across all cohorts for both drugs. Six patients (18.8%) reported an adverse event, all mild or moderate in intensity. No deaths or serious adverse events occurred. The single-dose PK of ceftazidime and avibactam were comparable between each of the 4 age cohorts investigated and were broadly similar to those previously observed in adults. No new safety concerns were identified. (This study has been registered at ClinicalTrials.gov under registration no. NCT01893346.)

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Phase 1 Study Assessing the Pharmacokinetic Profile and Safety of Avibactam in Patients With Renal Impairment.

Merdjan H[1], Tarral A[1], Das S[2], Li J[3].

Author information

Abstract

Avibactam is a non-β-lactam β-lactamase inhibitor intended for use as a fixed-dose combination with ceftazidime for the treatment of certain serious Gram-negative infections. As avibactam is primarily excreted unchanged in the urine, renal impairment may affect its pharmacokinetics. This phase 1 study investigated the effect of renal impairment and hemodialysis on avibactam pharmacokinetics and safety. Healthy controls and subjects with increasing degrees of renal impairment received a single 30-minute intravenous (IV) infusion of avibactam (100 mg). Anuric subjects requiring hemodialysis received the same infusion pre- and posthemodialysis, separated by a 7- to 14-day washout. Blood and urine samples were collected, and pharmacokinetics were analyzed using noncompartmental methods. The relationships between avibactam total plasma clearance (CL) or renal clearance (CL_R) and creatinine clearance (CrCL) were evaluated by linear correlation analysis. Safety was also monitored. Increasing severity of renal impairment was associated with decreasing CL and CL_R and increasing exposure and terminal half-life ($t_{1/2}$). Avibactam CL and CL_R demonstrated an approximately linear relationship with CrCL comparable to that previously observed for ceftazidime. In patients requiring hemodialysis, >50% of the administered avibactam was removed during a 4-hour hemodialysis session, demonstrating that avibactam should be administered after hemodialysis. No new safety findings were reported. To conclude, avibactam dose adjustment is warranted in patients with renal impairment based on the severity of impairment. Because the slope of the linear relationship between avibactam total plasma CL and CrCL is similar to that of ceftazidime, renal impairment dose adjustments should maintain the currently advised 4:1 ratio of ceftazidime:avibactam.

KEYWORDS: avibactam; ceftazidime; pharmacokinetic profile; renal impairment; safety; target attainment

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