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NOVÉ MOŽNOSTIANTIBIOTICKEJ LIEČBY Z POHĽADU INFEKTOLÓGA

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

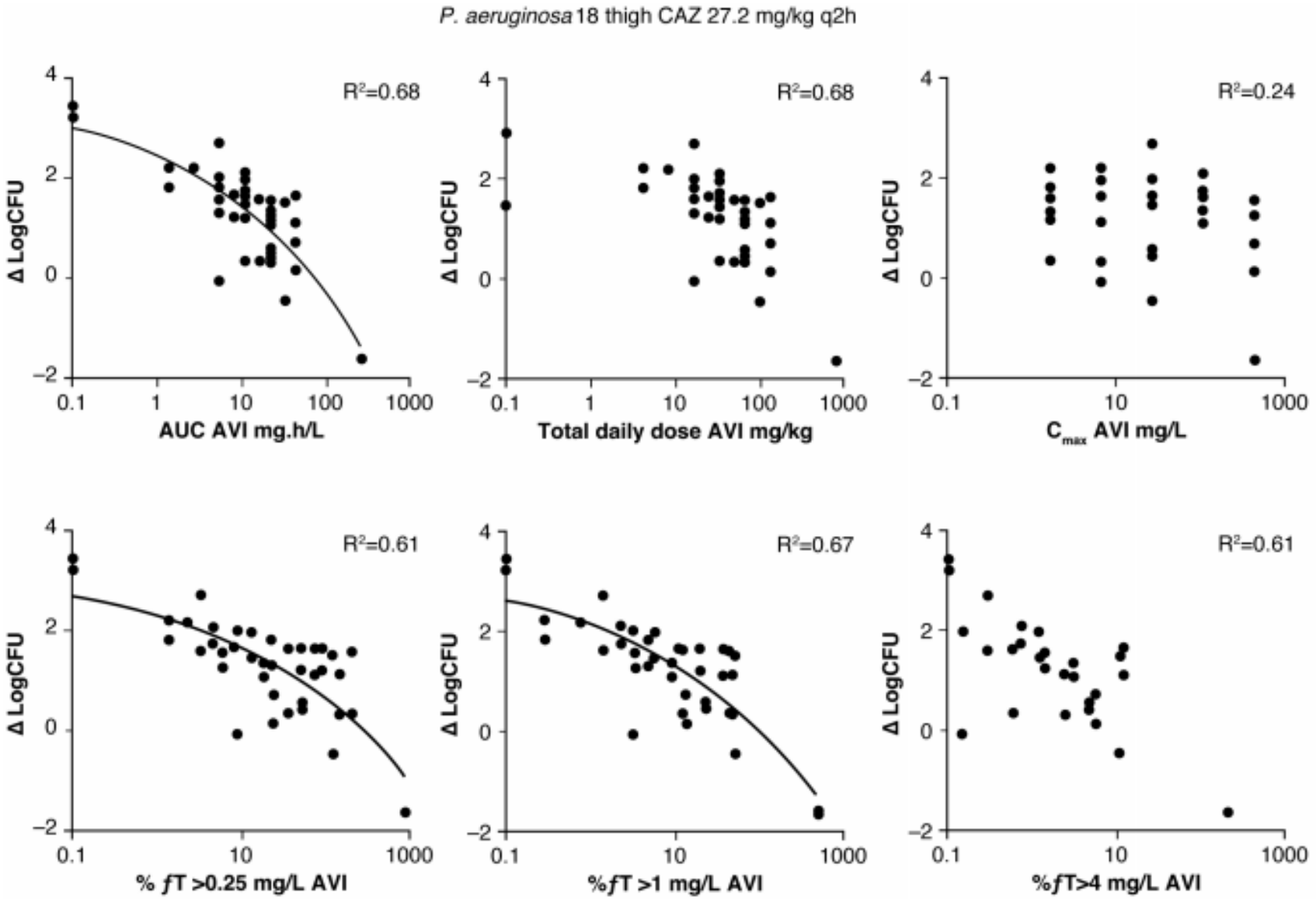


FIG 2 Dose fractionation study of avibactam in combination with ceftazidime against a ceftazidime-resistant *P. aeruginosa* strain in the neutropenic mouse thigh infection model.

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)

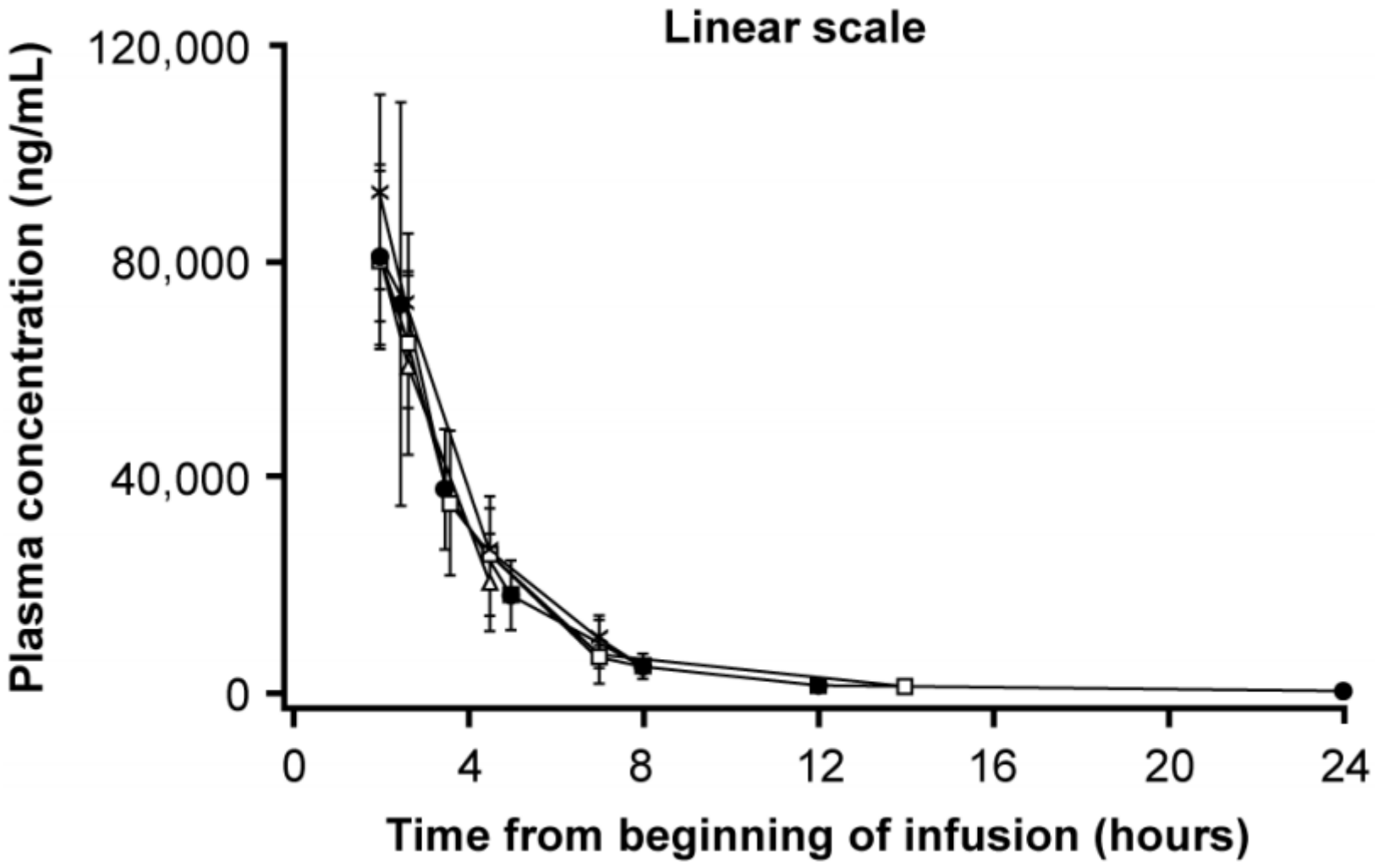
	Cohort 1 (≥12 yr to <18 yr) (*n* = 8)	Cohort 2 (≥6 yr to <12 yr) (*n* = 8)	Cohort 3 (≥2 yr to <6 yr) (*n* = 8)	Cohort 4 (≥3 m to <2 yr) (*n* = 8)
Ceftazidime[a]				
C_{max} (mg/l)	79.8 (41.8)	81.3 (17.8)	80.1 (14.7)[b]	91.7 (19.6)[b]
t_{max} (h)[c]	2.0 (1.9–2.6)	2.1 (1.9–2.4)	–	–
AUC_{0-t} (h·mg/l)	229.2 (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)

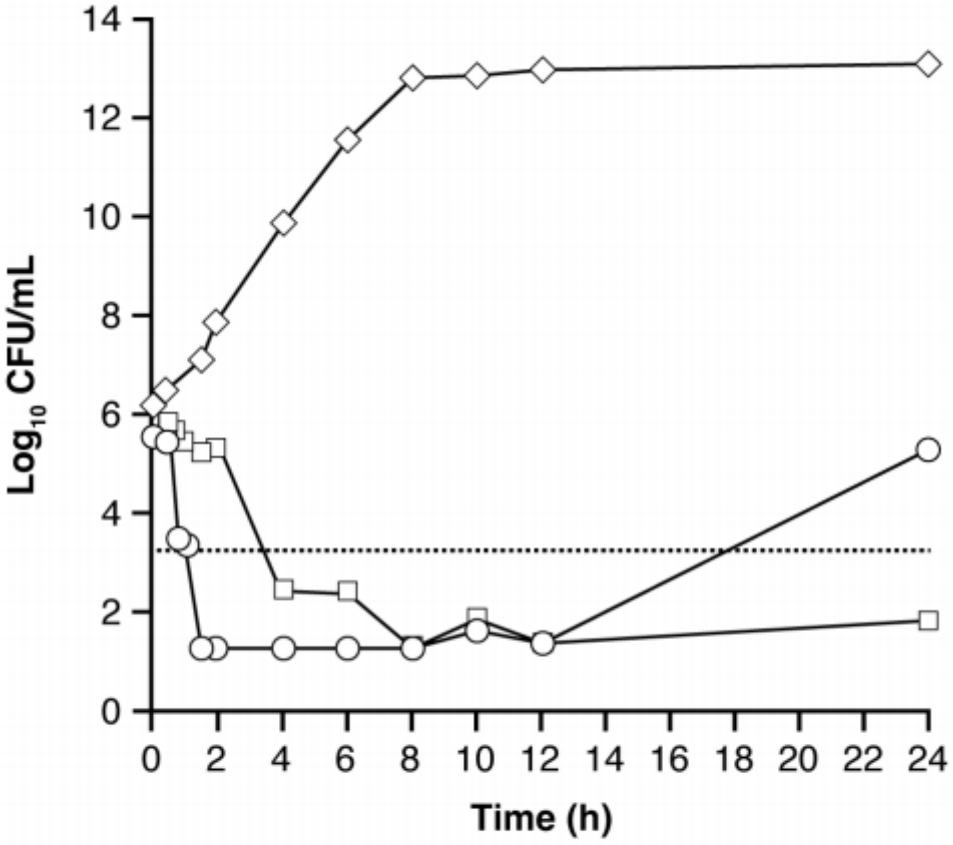


FIG 1 Responses of ceftazidime-resistant *E. cloacae* to continuous infusion of ceftazidime combined with two different concentration-time profiles of avibactam in the hollow fiber model.

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

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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

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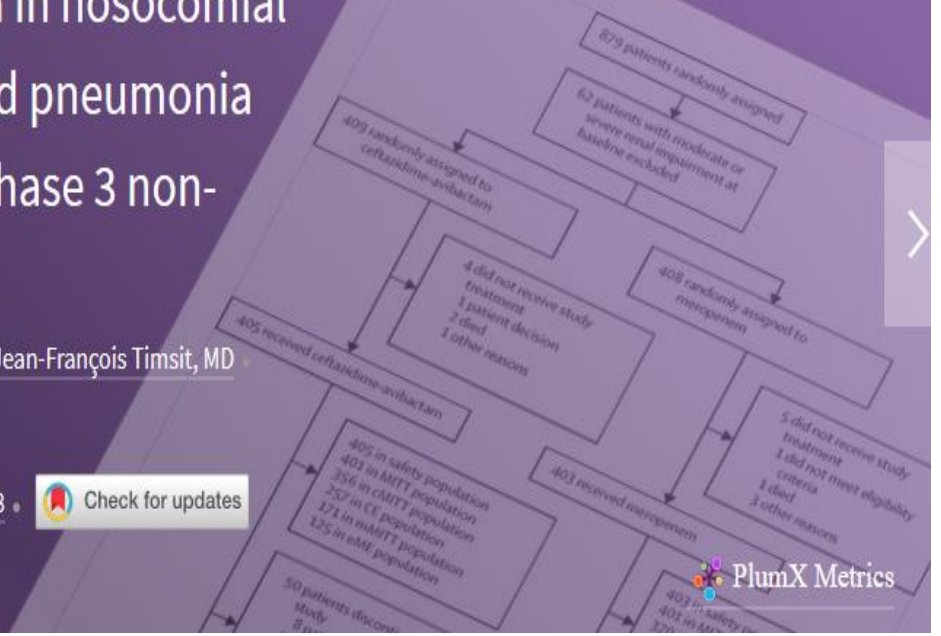
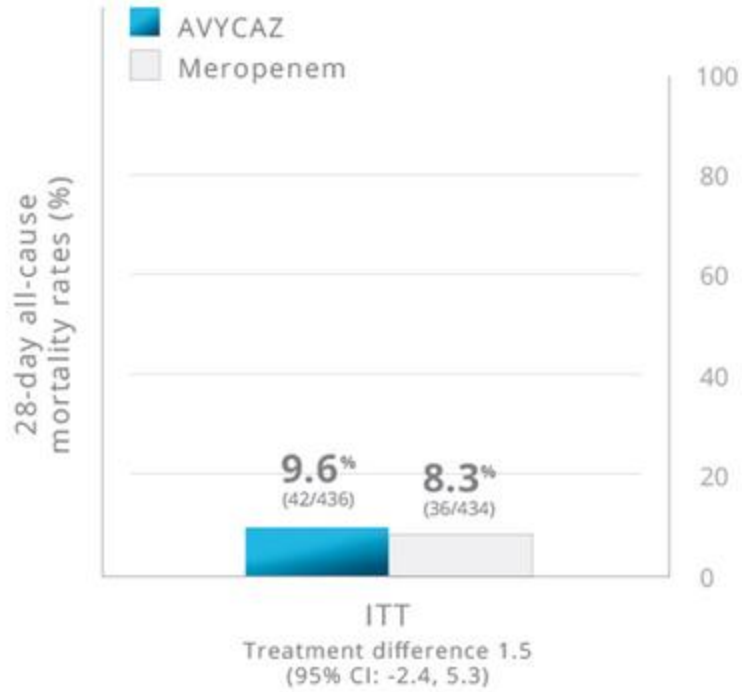
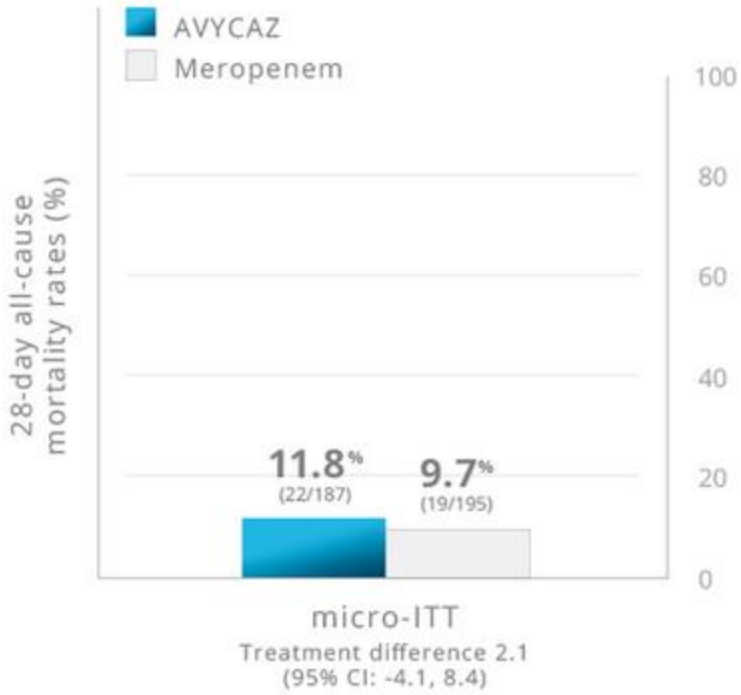


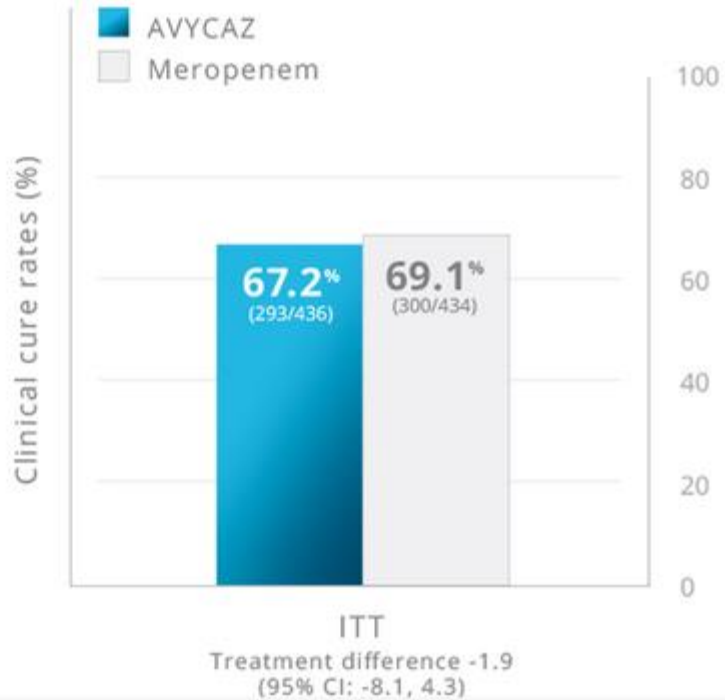
28-DAY ALL-CAUSE MORTALITY RATES (ITT)[1]



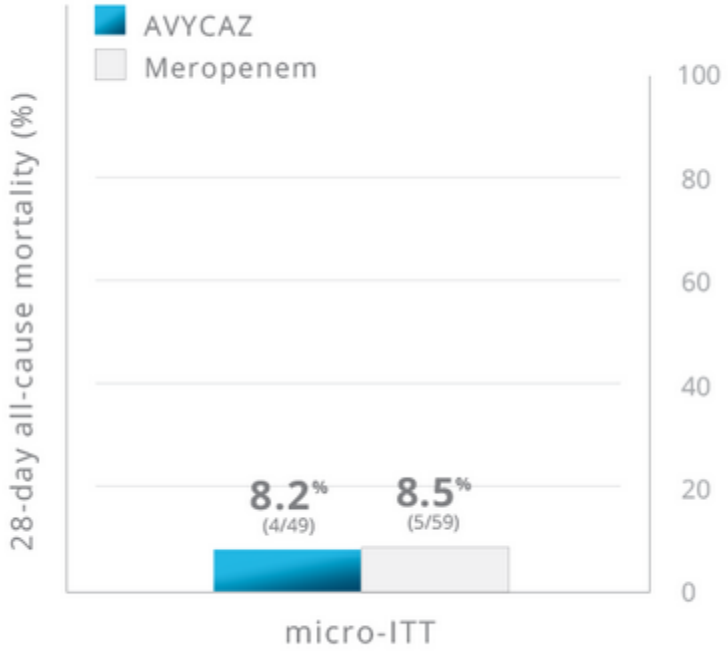
28-DAY ALL-CAUSE MORTALITY RATES (micro-ITT)[1]



CLINICAL CURE RATES AT TOC (ITT)*†‡[1]



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



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

NS, nonsusceptible.

micro-ITT, microbiological intent-to-treat.

Mortality data by pathogen

28-DAY ALL-CAUSE MORTALITY BY BASELINE PATHOGEN (micro-ITT)

	AVYCAZ	Meropenem
Enterobacteriaceae		
Klebsiella pneumoniae	**16.9%** (11/65)	**12.0%** (9/75)
Enterobacter cloacae	**0.0%** (0/29)	**17.4%** (4/23)
Escherichia coli	**18.2%** (4/22)	**13.0%** (3/23)
Serratia marcescens	**0.0%** (0/15)	**0.0%** (0/13)
Proteus mirabilis	**7.1%** (1/14)	**8.3%** (1/12)
Haemophilus influenzae	**6.3%** (1/16)	**8.0%** (2/25)
Pseudomonas aeruginosa	**14.1%** (9/64)	**7.8%** (4/51)

CLINICAL CURE RATES AT TOC BY BASELINE PATHOGEN (micro-ITT)[1]

	AVYCAZ	Meropenem
Enterobacteriaceae	**69.2%** (92/133)	**73.5%** (108/147)
Klebsiella pneumoniae	**67.7%** (44/65)	**74.7%** (56/75)
Enterobacter cloacae	**86.2%** (25/29)	**56.5%** (13/23)
Escherichia coli	**54.5%** (12/22)	**73.9%** (17/23)
Serratia marcescens	**73.3%** (11/15)	**92.3%** (12/13)
Proteus mirabilis	**85.7%** (12/14)	**75.0%** (9/12)
Haemophilus influenzae	**81.3%** (13/16)	**80.0%** (20/25)
Pseudomonas aeruginosa	**59.4%** (38/64)	**72.5%** (37/51)

TOC, test of cure.

micro-ITT, microbiological intent-to-treat.

cUTI Trial 1—RECAPTURE

cUTI Phase 3 clinical trial vs doripenem

STUDY DESIGN[1]

TYPE OF TRIAL	Phase 3, multinational, multicenter, double-blind, randomized, noninferiority trial
STUDY POPULATION	1020 adults hospitalized with cUTI, which included acute pyelonephritis and complicated lower urinary tract infections. The microbiologically modified intent-to-treat (mMITT) population, which included all patients who had at least one uropathogen isolated at baseline ($\geq 10^5$ CFU/mL), consisted of 810 patients; the median age was 55 years, and 69.8% were female.
COMPARATIVE AGENTS	AVYCAZ® 2.5 g (ceftazidime 2 grams and avibactam 0.5 grams) IV every 8 hours Doripenem 0.5 grams IV every 8 hours A switch to an oral antimicrobial agent was allowed after 5 days of IV dosing.

Clinical Infectious Diseases

MAJOR ARTICLE

Ceftazidime-avibactam Versus Doripenem for the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis: RECAPTURE, a Phase 3 Randomized Trial Program

Florian M. Wagenlehner,[1] Jack D. Sobel,[2] Paul Newell,[3] Jon Armstrong,[3] Xiangning Huang,[4] Gregory G. Stone,[5] Katrina Yates,[3,a] and Leanne B. Gasink[6,b]

[1]Justus-Liebig-University, Giessen, Germany; [2]Detroit Medical Center, Michigan; [3]AstraZeneca, Alderley Park, Cheshire, and [4]AstraZeneca, Cambridge, United Kingdom; [5]AstraZeneca, Waltham, Massachusetts; and [6]AstraZeneca, Wilmington, Delaware

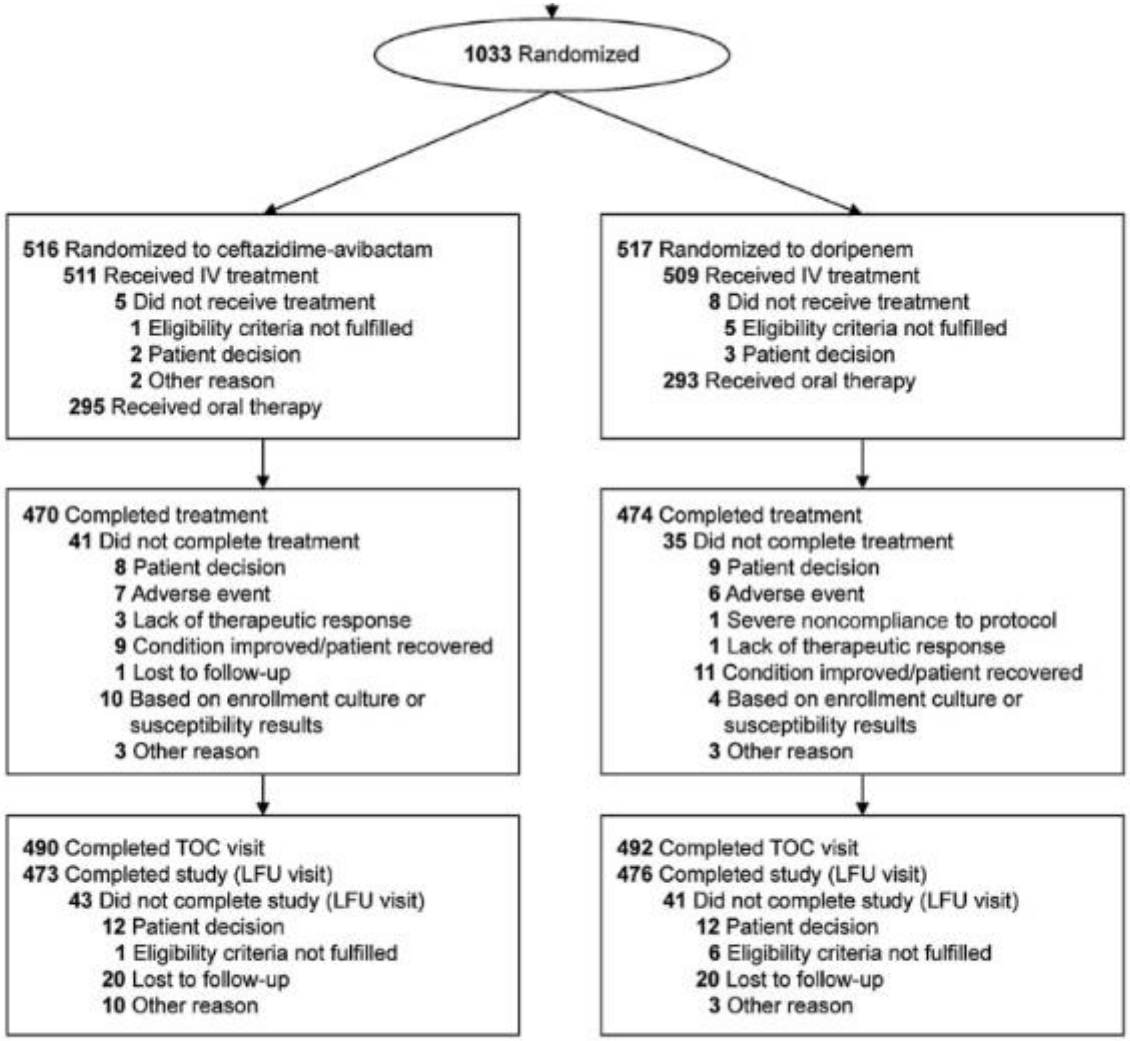


Figure 1. Flow of patients in the RECAPTURE trials. Abbreviations: IV, intravenous; LFU, late follow-up (45–52 days after randomization); TOC, test of cure (21–25 days after randomization).

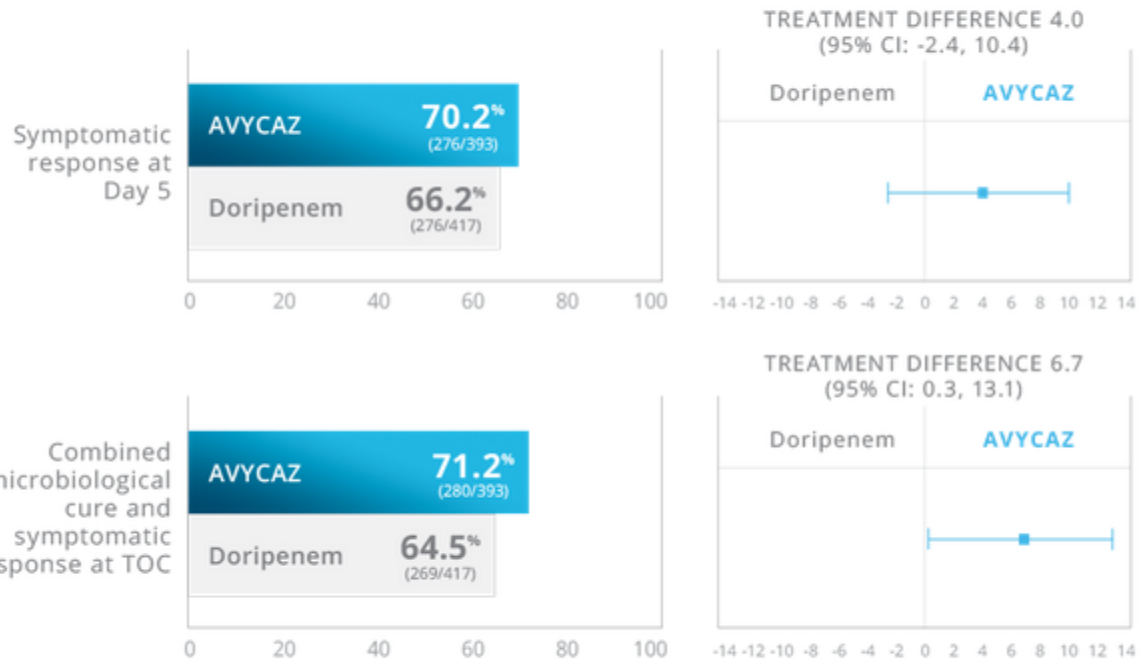
Table 1. Baseline Patient Characteristics (Microbiological Modified Intent-to-Treat Population)

Characteristic	Ceftazidime-Avibactam (n = 393)	Doripenem (n = 417)
Age, y, mean (SD)	51.4 (20.2)	53.3 (18.6)
Male	121 (30.8)	124 (29.7)
Race		
White	321 (81.7)	351 (84.2)
Black or African American	1 (0.3)	4 (1.0)
Asian	35 (8.9)	28 (6.7)
American Indian or Alaska Native	1 (0.3)	3 (0.7)
Other	35 (8.9)	31 (7.4)
Body mass index, kg/m^2, mean (SD)	26.2 (5.9)	26.3 (5.6)
Diagnosis		
cUTI without pyelonephritis	106 (27.0)	121 (29.0)
Pyelonephritis	287 (73.0)	296 (71.0)
With ≥1 complicating factor	41 (10.4)	39 (9.4)
Meeting symptom criteria for cUTI	33 (8.4)	31 (7.4)
Bacteremia	38 (9.7)	33 (7.9)
Fever	157 (39.9)	150 (36.0)
White blood cell count, 10^9/mL, median (range)	8.5 (3.3–27.8)	7.9 (3.1–35.4)
CrCl, mL/min, mean (SD)[a]	87.6 (34.5)	85.9 (34.5)
Renal status		
Normal renal function/mild impairment (CrCl >50 mL/min)	350 (89.1)	379 (90.9)
Moderate impairment (CrCl 31–50 mL/min)	42 (10.7)	35 (8.4)
Severe impairment (CrCl <31 mL/min)	1 (0.3)	3 (0.7)
Baseline pathogen in urine[b]		
Enterobacteriaceae	376 (95.7)	396 (95.0)
Escherichia coli	292 (74.3)	306 (73.4)
Klebsiella pneumoniae	44 (11.2)	56 (13.4)
Proteus mirabilis	17 (4.3)	13 (3.1)
Enterobacter cloacae	11 (2.8)	13 (3.1)
ESBL-positive Enterobacteriaceae	73 (18.6)	82 (19.7)
Other gram-negative bacteria	18 (4.6)	21 (5.0)
Pseudomonas aeruginosa	18 (4.6)	20 (4.8)
Prior systemic antibiotic use	28 (7.1)	27 (6.5)

Clinical efficacy in cUTI demonstrated in a Phase 3 trial vs doripenem[1]

- AVYCAZ was noninferior to doripenem with regard to both primary endpoints[1]

CLINICAL AND MICROBIOLOGICAL CURE RATES (mMITT)[1]



mMITT, microbiologically modified intent-to-treat.

CI, confidence interval.

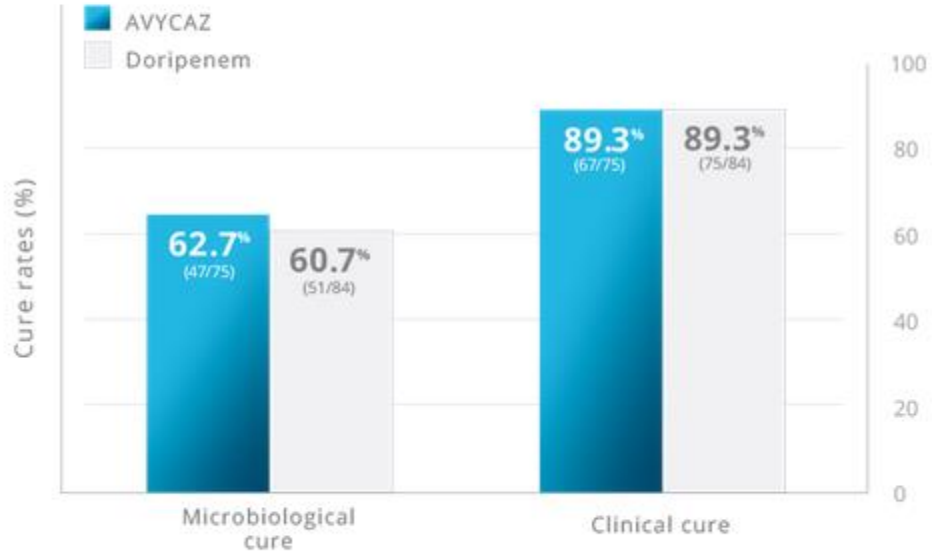
TOC, test of cure.

Subset populations

Clinical efficacy in cUTI caused by ceftazidime-NS Gram-negative pathogens[1]

- At baseline, 75 patients in the AVYCAZ arm and 84 patients in the doripenem arm of the mMITT population had Gram-negative isolates that were not susceptible to ceftazidime[1]

CEFTAZIDIME-NS SUBSET POPULATION: MICROBIOLOGICAL AND CLINICAL CURE RATES AT TOC (mMITT)[1]



NS, nonsusceptible.

TOC, test of cure.

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 2. Summary of Primary and Secondary Efficacy Endpoints (Microbiological Modified Intent-to-Treat Population)

Endpoint	Patients, No. (%)		Difference, % (95% CI)
	Ceftazidime-Avibactam (n = 393)	Doripenem (n = 417)	
FDA co-primary endpoints			
Patient-assessed symptomatic resolution[a] at day 5[b]	276 (70.2)	276 (66.2)	4.0 (−2.39 to 10.42)
Combined patient-assessed symptomatic resolution[c] and favorable per-patient microbiological response at TOC[b]	280 (71.2)	269 (64.5)	6.7 (.30 to 13.12)
Per-patient favorable microbiological response at TOC	304 (77.4)	296 (71.0)	6.4 (.33 to 12.36)
Patient-reported symptomatic resolution at TOC	332 (84.5)	360 (86.3)	−1.9 (−6.78 to 3.02)
EMA primary endpoint			
Per-patient favorable microbiological response at TOC[d]	304 (77.4)	296 (71.0)	6.4 (.33 to 12.36)
Secondary endpoints			
Microbiological			
Per-patient favorable microbiological response at EOT (IV)	374 (95.2)	395 (94.7)	0.4 (−2.7 to 3.56)
Per-patient favorable microbiological response at LFU	268 (68.2)	254 (60.9)	7.3 (.68 to 13.81)
Per-patient favorable microbiological response at TOC in patients with a ceftazidime-nonsusceptible pathogen[e]	47/75 (62.7)	51/84[f] (60.7)	2.0 (−13.18 to 16.89)
Per-patient favorable microbiological response at LFU in patients with a ceftazidime-nonsusceptible pathogen[e]	46/75 (61.3)	38/84 (45.2)	16.1 (.50 to 30.89)
Per-patient favorable microbiological response at TOC in patients with a ceftazidime-susceptible pathogen[c]	256/316 (81.0)	238/326 (73.0)	8.0 (1.50 to 14.48)
Per-patient favorable microbiological response at LFU in patients with a ceftazidime-susceptible pathogen[e]	221/316 (69.9)	209/326 (64.1)	5.8 (−1.46 to 13.05)
Clinical			
Investigator-determined clinical cure			
EOT (IV)	378 (96.2)	407 (97.6)	−1.4 (−4.07 to 1.02)
TOC	355 (90.3)	377 (90.4)	−0.1 (−4.23 to 4.03)
LFU	335 (85.2)	350 (83.9)	1.3 (−3.71 to 6.30)
Sustained clinical cure at LFU in patients who were cured at TOC	330/355 (93.0)	345/377 (91.5)	1.4 (−2.5 to 5.4)
Investigator-determined clinical cure at TOC in patients with a ceftazidime-susceptible pathogen[e]	287/316 (90.8)	295/326 (90.5)	0.3 (−4.3 to 4.9)
Investigator-determined clinical cure at TOC in patients with a ceftazidime-nonsusceptible pathogen[e]	67/75 (89.3)	75/84[f] (89.3)	0.0 (−10.4 to 10.1)

Denominators are the total numbers in each group unless shown otherwise.

Abbreviations: CI, confidence interval; EMA, European Medicines Agency; EOT (IV), end of intravenous therapy; FDA, US Food and Drug Administration; LFU, late follow-up (45–52 days after randomization); TOC, test of cure (21–25 days after randomization).

[a] Symptomatic resolution of symptoms of frequency, urgency, dysuria, and suprapubic pain with resolution or improvement in flank pain, based on the patient-reported symptom assessment questionnaire (PSAQ).

cUTI Trial 2—REPRISE

STUDY DESIGN[1]

TYPE OF TRIAL	Multinational, multicenter, randomized, open-label trial
STUDY POPULATION	305 adults hospitalized with cUTI, including acute pyelonephritis and complicated lower urinary tract infections, due to ceftazidime-nonsusceptible Gram-negative pathogens. The mMITT population consisted of 281 cUTI patients with at least one baseline ceftazidime-NS uropathogen (defined as MIC greater or equal to 8 mg/L for Enterobacteriaceae and greater or equal to 16 mg/L for *P. aeruginosa*). The median age was 65 years and 54.8% were male.
COMPARATIVE AGENTS	AVYCAZ® 2.5 g (ceftazidime 2 grams and avibactam 0.5 grams) IV every 8 hours Best available IV therapy (BAT)—meropenem, imipenem, doripenem, and colistin—for 5 to 21 days of total therapy. The majority (96.1%) of patients in the BAT arm received monotherapy with a carbapenem antibiotic. There was no optional switch to oral therapy.

THE LANCET
Infectious Diseases

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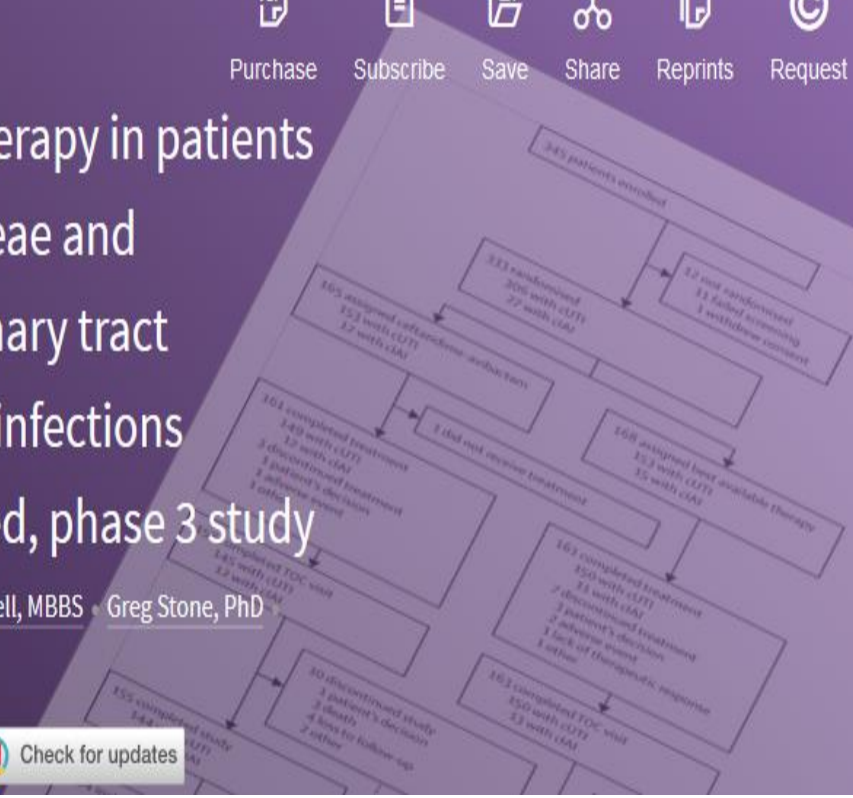
Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study

Prof Yehuda Carmeli, MD • Jon Armstrong, MSc • Peter J Laud, MSc • Paul Newell, MBBS • Greg Stone, PhD • Angela Wardman, BPharm • Leanne B Gasink, MD

Published: April 20, 2016 • DOI: https://doi.org/10.1016/S1473-3099(16)30004-4 • Check for updates

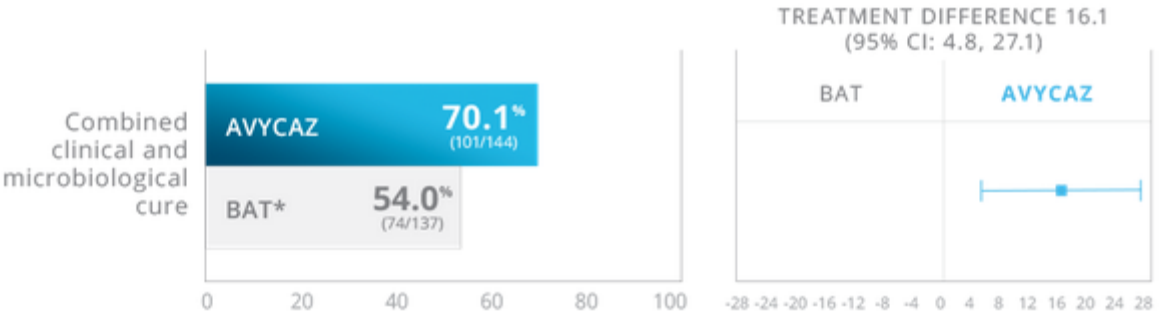


In a trial vs carbapenems and colistin...

Clinical efficacy demonstrated in cUTI caused by ceftazidime-NS Gram-negative pathogens[1]

- AVYCAZ demonstrated a higher cure rate with regard to the combined clinical and microbiological cure vs best available therapy (BAT)* at the Day 21 to 25 visit[1]

COMBINED CLINICAL AND MICROBIOLOGICAL CURE RATES AT THE DAY 21 TO 25 VISIT (mMITT)[1]



* Best available therapy (BAT) options were meropenem, imipenem, doripenem, and colistin; the majority of patients received carbapenem monotherapy.[1]

NS, nonsusceptible.

mMITT, microbiologically modified intent-to-treat.

CI, confidence interval.

- Clinical cure at the Day 21 to 25 visit was 88.2% (127/144) for AVYCAZ and 88.3% (121/137) for BAT, a treatment difference of -0.1 (95% CI: -7.9, 7.7)[1]
- Microbiological cure at the Day 21 to 25 visit was 71.5% (103/144) for AVYCAZ and 56.9% (78/137) for BAT, a treatment difference of 14.6 (95% CI: 3.4, 25.5)[1]

Subset population

Clinical efficacy demonstrated in cUTI involving ESBLs and AmpC, including KPC-producing CRE[1]

- In a subset of Gram-negative uropathogens, genotypic testing identified certain ESBL groups and AmpC in 97.2% (273/281) of patients in the mMITT population, all of which were expected to be inhibited by avibactam[1]:

KPC-2	KPC-3	TEM-1	SHV-12	CTX-M-15	CTX-M-27	OXA-48	AmpC

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

ESBLs, extended-spectrum β-lactamases.

KPC, *Klebsiella pneumoniae* carbapenemase.

CRE, carbapenem-resistant Enterobacteriaceae.

mMITT, microbiologically modified intent-to-treat.

Clinical efficacy in cUTI across baseline ceftazidime-NS Gram-negative pathogens[1]

MICROBIOLOGICAL RESPONSE RATES BY BASELINE CEFTAZIDIME-NS PATHOGEN AT THE DAY 21 TO 25 VISIT (mMITT)[1]

	AVYCAZ®	BAT
Enterobacteriaceae		
Escherichia coli	**76.3%** (45/59)	**57.9%** (33/57)
Klebsiella pneumoniae	**76.4%** (42/55)	**60.0%** (39/65)
Pseudomonas aeruginosa	**57.1%** (8/14)	**60.0%** (3/5)

NS, nonsusceptible.

mMITT, microbiologically modified intent-to-treat.

BAT, best available therapy.

Curr Med Res Opin. 2012 Dec;28(12):1921-31. doi: 10.1185/03007995.2012.748653. Epub 2012 Nov 21.

Efficacy and safety of ceftazidime-avibactam versus imipenem-cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: results of a prospective, investigator-blinded, randomized study.

Vazquez JA[1], González Patzán LD, Stricklin D, Duttaroy DD, Kreidly Z, Lipka J, Sable C.

Author information

Abstract

OBJECTIVES: The aim of this prospective phase II, randomized, investigator-blinded study (NCT00690378) was to compare the efficacy and safety of ceftazidime-avibactam and imipenem-cilastatin in hospitalized adults with serious complicated urinary tract infection (cUTI) due to Gram-negative pathogens.

PATIENTS AND METHODS: Patients aged between 18 and 90 years with cUTI were enrolled and stratified by infection type (acute pyelonephritis or other cUTI) and randomized 1:1 to receive intravenous ceftazidime 500 mg plus avibactam 125 mg every 8 hours or imipenem-cilastatin 500 mg every 6 hours. Patients meeting pre-specified improvement criteria after 4 days could be switched to oral ciprofloxacin. Patients were treated for a total of 7-14 days. The primary efficacy objective was a favorable microbiological response at the test-of-cure (TOC) visit 5-9 days post-therapy in microbiologically evaluable (ME) patients.

RESULTS: Overall, 135 patients received study therapy (safety population); 62 were included in the ME population (ceftazidime-avibactam, n = 27; imipenem-cilastatin, n = 35). The predominant uropathogen was Escherichia coli. Favorable microbiological response was achieved in 70.4% of ME patients receiving ceftazidime-avibactam and 71.4% receiving imipenem-cilastatin at the TOC visit (observed difference -1.1% [95% CI: -27.2%, 25.0%]). Among ME patients with ceftazidime-resistant uropathogens, response was observed in 6/7 (85.7%) receiving ceftazidime-avibactam. Adverse events were observed in 67.6% and 76.1% of patients receiving ceftazidime-avibactam and imipenem-cilastatin, respectively. Limitations of the study include the small number of patients in the ME population.

CONCLUSION: The results suggest that the efficacy and safety of ceftazidime-avibactam may be similar to that of imipenem-cilastatin.

PMID: 23145859 DOI: 10.1185/03007995.2012.748653

[Indexed for MEDLINE]

cIAI Trial—RECLAIM

cIAI Phase 3 clinical trial vs meropenem

STUDY DESIGN[1]

TYPE OF TRIAL	Phase 3, multinational, double-blind, noninferiority trial
STUDY POPULATION	1058 adults hospitalized with cIAI, which included appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, perforation of the intestine, and other causes of intra-abdominal abscesses and peritonitis. The microbiologically modified intent-to-treat (mMITT) population, which included all patients who had at least one baseline intra-abdominal pathogen regardless of the susceptibility to study drug, consisted of 823 patients; the median age was 51 years and 62.8% were male.
COMPARATIVE AGENTS	AVYCAZ® 2.5 g (2 g ceftazidime and 0.5 g avibactam) IV every 8 hours plus metronidazole 0.5 g IV every 8 hours

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A randomised, double-blind, phase 3 study comparing the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem for complicated intra-abdominal infections in hospitalised adults in Asia

Xinyu Qin [a], Binh Giang Tran [b], Min Ja Kim [c], Lie Wang [d], Dung Anh Nguyen [e], Qian Chen [f], Jie Song [g,*], Peter J. Laud [h], Gregory G. Stone [i,1], Joseph W. Chow [j]

[a] *Zhongshan Hospital affiliated to Fudan University, Shanghai, China*
[b] *Viet-Duc Hospital, Hanoi, Viet Nam*
[c] *Korea University Anam Hospital, Seoul, Republic of Korea*
[d] *Fuzhou General Hospital of Nanjing Military Region, Fuzhou, China*
[e] *Gia Dinh People Hospital, Ho Chi Minh, Viet Nam*
[f] *Affiliated Hospital of Guilin Medical University, Guangxi, China*
[g] *Global Medicines Development, AstraZeneca, 199 Liangjing Road, Zhangjiang Hi-tech Park, Shanghai 201203, China*
[h] *Statistical Services Unit, University of Sheffield, Sheffield, UK*
[i] *AstraZeneca, Waltham, MA, USA*
[j] *AstraZeneca, Wilmington, DE, USA*

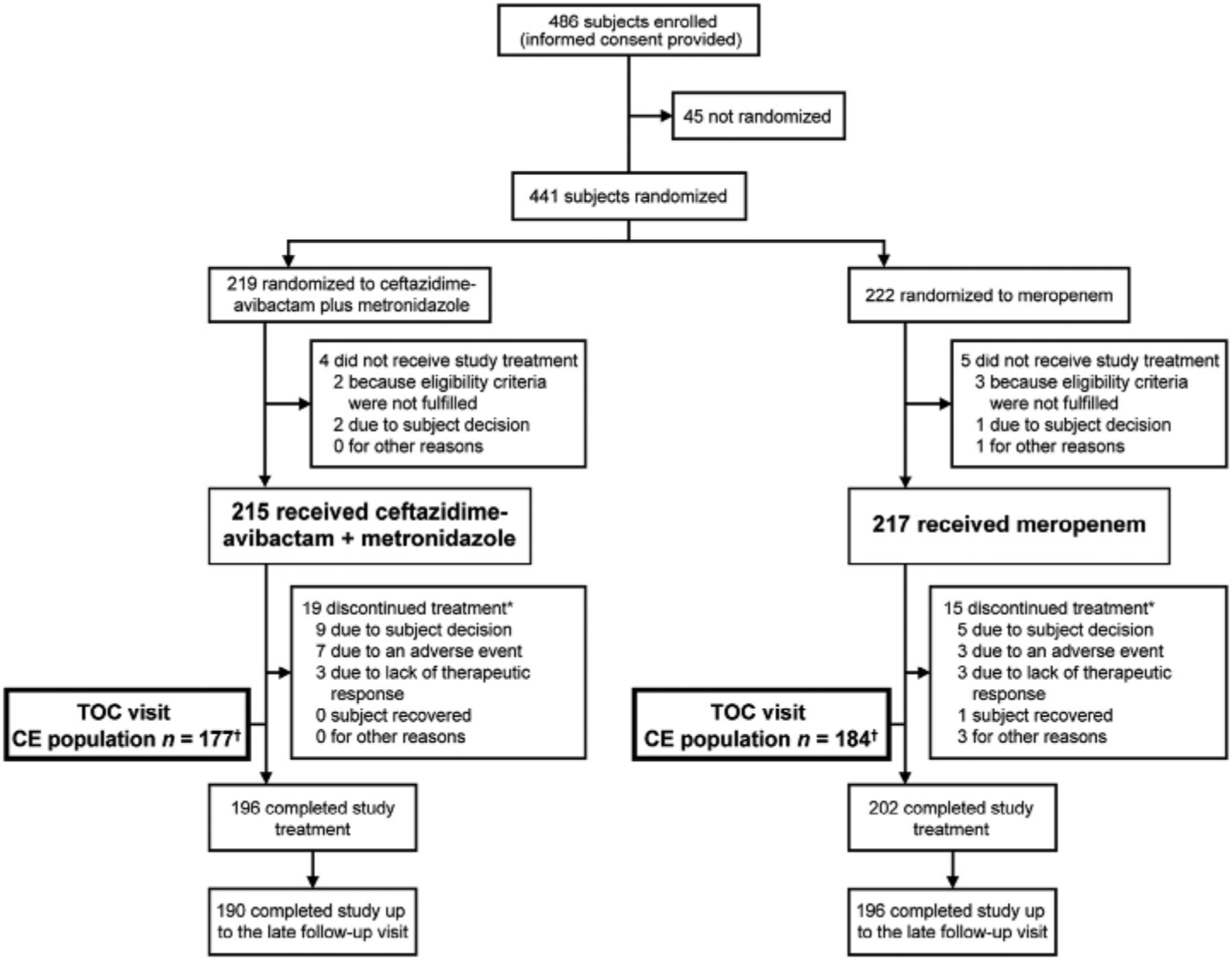

486 subjects enrolled (informed consent provided)
45 not randomized
441 subjects randomized
219 randomized to ceftazidime-avibactam plus metronidazole
222 randomized to meropenem
4 did not receive study treatment
2 because eligibility criteria were not fulfilled
2 due to subject decision
0 for other reasons
5 did not receive study treatment
3 because eligibility criteria were not fulfilled
1 due to subject decision
1 for other reasons
215 received ceftazidime-avibactam + metronidazole
217 received meropenem
19 discontinued treatment*
9 due to subject decision
7 due to an adverse event
3 due to lack of therapeutic response
0 subject recovered
0 for other reasons
15 discontinued treatment*
5 due to subject decision
3 due to an adverse event
3 due to lack of therapeutic response
1 subject recovered
3 for other reasons
TOC visit CE population n = 177†
TOC visit CE population n = 184†
196 completed study treatment
202 completed study treatment
190 completed study up to the late follow-up visit
196 completed study up to the late follow-up visit

Table 2
Baseline patient and disease characteristics (modified intention-to-treat population)[a].

Parameter	Ceftazidime/avibactam + metronidazole ($n = 214$)	Meropenem ($n = 217$)
Age (years) (mean ± S.D.)	48.5 ± 16.8	48.5 ± 17.4
Sex male	141 (65.9)	153 (70.5)
Asian	214 (100)	217 (100)
Chinese	127 (59.3)	135 (62.2)
BMI (kg/m^2) (mean ± S.D.)	22.7 ± 3.5	22.4 ± 3.5
APACHE II score		
≤10	201 (93.9)	201 (92.6)
>10 to ≤30	13 (6.1)	16 (7.4)
Primary diagnosis		
Appendiceal perforation or periappendiceal abscess	83 (38.8)	79 (36.4)
Secondary peritonitis	36 (16.8)	38 (17.5)
Cholecystitis	33 (15.4)	27 (12.4)
Intra-abdominal abscess	22 (10.3)	24 (11.1)
Acute gastric and duodenal perforations	22 (10.3)	23 (10.6)
Traumatic perforations	13 (6.1)	17 (7.8)
Diverticular disease	5 (2.3)	9 (4.1)
Prior treatment failure	26 (12.1)	27 (12.4)
Systemic antimicrobial therapy in the previous 72 h before randomisation	167 (78.0)	172 (79.3)
≤24 h exposure	139 (65.0)	143 (65.9)
Infection type		
Monomicrobial infection	84 (39.3)	101 (46.5)
Polymicrobial infection	58 (27.1)	52 (24.0)
No study-qualifying pathogen identified	72 (33.6)	64 (29.5)
Bacteraemia	5 (2.3)	10 (4.6)
Renal status		
Normal renal function/mild impairment (CrCL >50 mL/min)	201 (93.9)	201 (92.6)
Moderate impairment (CrCL >30 to ≤50 mL/min)	13 (6.1)	16 (7.4)

S.D., standard deviation; BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; CrCL, creatinine clearance.
[a] Data are *n* (%) unless otherwise stated.

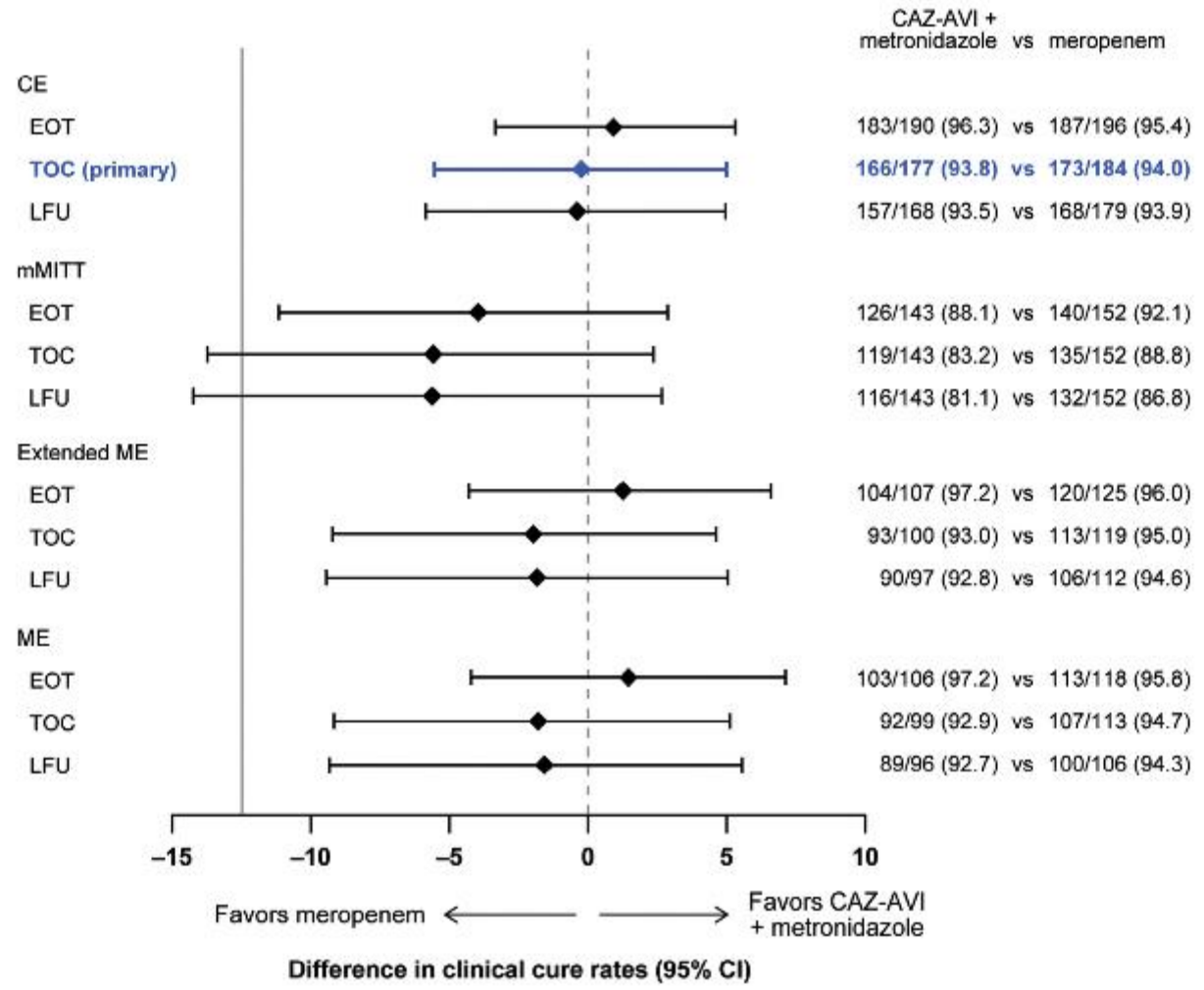
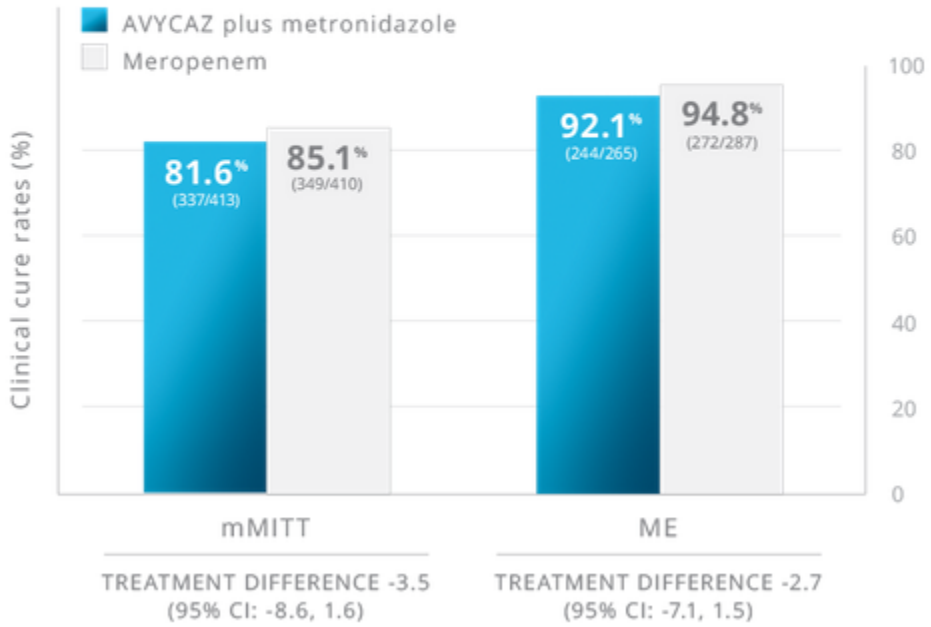


Fig. 2. Difference in clinical cure rate with ceftazidime/avibactam (CAZ-AVI) plus metronidazole compared with meropenem by visit and analysis population. CE, clinically evaluable; EOT, end-of-treatment; TOC, test-of-cure; LFU, late follow-up; mMITT, microbiologically modified intention-to-treat; ME, microbiologically evaluable; CI, confidence interval. Data listed are *n*/*N* (%). Solid vertical line represents –12.5% non-inferiority margin.

Clinical efficacy in cIAI demonstrated in a Phase 3 trial vs meropenem[1]

- AVYCAZ plus metronidazole was noninferior to meropenem with regard to the clinical cure rate at the TOC visit in the mMITT population[1]

CLINICAL CURE RATES AT TOC (mMITT and ME*)[1]



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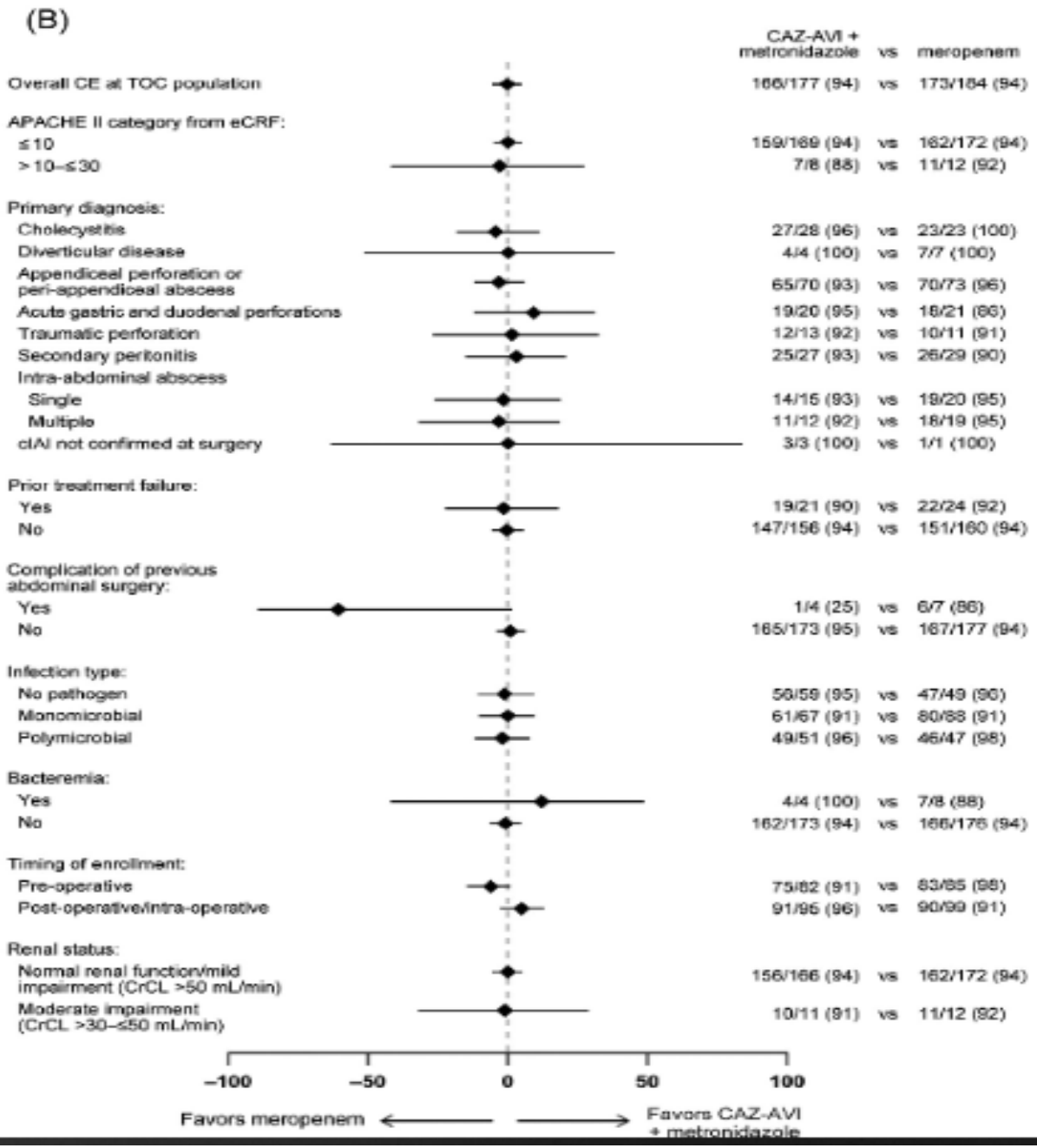

(B)
CAZ-AVI + metronidazole
vs
meropenem
Overall CE at TOC population
166/177 (94) vs 173/184 (94)
APACHE II category from eCRF:
≤ 10
159/169 (94) vs 162/172 (94)
> 10–≤ 30
7/8 (88) vs 11/12 (92)
Primary diagnosis:
Cholecystitis
27/28 (96) vs 23/23 (100)
Diverticular disease
4/4 (100) vs 7/7 (100)
Appendiceal perforation or peri-appendiceal abscess
65/70 (93) vs 70/73 (96)
Acute gastric and duodenal perforations
19/20 (95) vs 16/21 (86)
Traumatic perforation
12/13 (92) vs 10/11 (91)
Secondary peritonitis
25/27 (93) vs 26/29 (90)
Intra-abdominal abscess
Single
14/15 (93) vs 19/20 (95)
Multiple
11/12 (92) vs 18/19 (95)
cIAI not confirmed at surgery
3/3 (100) vs 1/1 (100)
Prior treatment failure:
Yes
19/21 (90) vs 22/24 (92)
No
147/156 (94) vs 151/160 (94)
Complication of previous abdominal surgery:
Yes
1/4 (25) vs 6/7 (86)
No
165/173 (95) vs 167/177 (94)
Infection type:
No pathogen
56/59 (95) vs 47/49 (96)
Monomicrobial
61/67 (91) vs 60/68 (91)
Polymicrobial
49/51 (96) vs 46/47 (98)
Bacteremia:
Yes
4/4 (100) vs 7/8 (88)
No
162/173 (94) vs 166/176 (94)
Timing of enrollment:
Pre-operative
75/82 (91) vs 83/85 (98)
Post-operative/Intra-operative
91/95 (96) vs 90/99 (91)
Renal status:
Normal renal function/mild impairment (CrCL >50 mL/min)
156/166 (94) vs 162/172 (94)
Moderate impairment (CrCL >30–≤50 mL/min)
10/11 (91) vs 11/12 (92)
−100
−50
0
50
100
Favors meropenem
Favors CAZ-AVI + metronidazole

Table 3
Clinical response at the test-of-cure visit for subjects with ceftazidime-non-susceptible (CAZ-NS) and ceftazidime-susceptible (CAZ-S) Gram-negative pathogens [extended microbiologically evaluable (eME) population].

Isolates	Susceptibility	Ceftazidime/avibactam + metronidazole ($N = 100$)		Meropenem ($N = 119$)		Comparison between groups [difference[a], % (95% CI[b])]
		n	Clinical cure [*n* (%)]	*n*	Clinical cure [*n* (%)]	
All isolates	CAZ-NS	23	22 (95.7)	26	25 (96.2)	−0.5 (−17.93, 15.43)
	CAZ-S	76	70 (92.1)	89	84 (94.4)	−2.3 (−11.30, 5.82)
Enterobacteriaceae	CAZ-NS	21	20 (95.2)	25	24 (96.0)	−0.8 (−19.51, 15.78)
	CAZ-S	70	64 (91.4)	81	78 (96.3)	−4.9 (−14.28, 3.08)
Escherichia coli	CAZ-NS	14	13 (92.9)	23	22 (95.7)	−2.8 (−28.19, 15.54)
	CAZ-S	54	50 (92.6)	53	51 (96.2)	−3.6 (−14.40, 6.40)
Klebsiella pneumoniae	CAZ-NS	3	3 (100)	1	1 (100)	0.0 (−63.06, 83.67)
	CAZ-S	16	15 (93.8)	26	25 (96.2)	−2.4 (−25.36, 14.04)
Non-Enterobacteriaceae	CAZ-NS	2	2 (100)	1	1 (100)	0.0 (−74.23, 85.21)
	CAZ-S	15	15 (100)	15	13 (86.7)	13.3 (−9.08, 38.36)
Pseudomonas aeruginosa	CAZ-NS	1	1 (100)	0	0	–
	CAZ-S	10	10 (100)	14	12 (85.7)	14.3 (−16.23, 40.56)

[a] Difference in clinical cure rates (%).

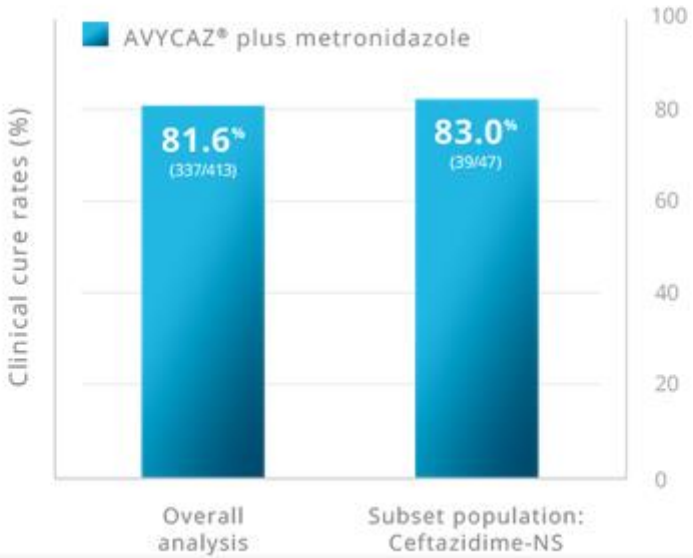
[b] 95% confidence interval (CI) for group differences was calculated using the unstratified Miettinen & Nurminen method. Clinical cure rate for the eME population was defined as the number of subjects with a response of clinical cure at the test-of-cure visit divided by the number of subjects with clinical cure + clinical failure. Clinical response was based on surgical review evaluation if it was different from the investigator's assessment. Ceftazidime resistance includes both the Clinical and Laboratory Standards Institute breakpoint-defined non-susceptible and intermediate categories [24]. Percentages are based on the total number of subjects in the subgroup (*n*).

Subset populations

Clinical efficacy in cIAI caused by ceftazidime-NS Gram-negative pathogens[1]

- At baseline, 111 patients in the mMITT population had Gram-negative isolates that were not susceptible to ceftazidime, including 61 patients with *E. coli* and 26 patients with *K. pneumoniae*[1]

CLINICAL CURE RATES AT TOC (mMITT): OVERALL ANALYSIS POPULATION AND CEFTAZIDIME-NS SUBSET POPULATION[1]



Clinical efficacy in cIAI involving ESBLs and AmpC[1]

- In a subset of Gram-negative pathogens from the Phase 3 cIAI trial, genotypic testing identified certain ESBL groups and AmpC in 12.8% (105/823) of patients in the mMITT population, all of which were expected to be inhibited by avibactam[1]:

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

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

ESBLs, extended-spectrum β-lactamases.

mMITT, microbiologically modified intent-to-treat.

Clinical data by pathogen

CLINICAL CURE RATES BY BASELINE PATHOGEN AT TOC (mMITT)[1]

	AVYCAZ plus metronidazole	Meropenem
Enterobacteriaceae	**81.4%** (272/334)	**86.4%** (305/353)
Escherichia coli	**80.4%** (218/271)	**87.0%** (248/285)
Klebsiella pneumoniae	**78.4%** (40/51)	**75.5%** (37/49)
Klebsiella oxytoca	**77.8%** (14/18)	**80.0%** (12/15)
Enterobacter cloacae	**84.6%** (11/13)	**84.2%** (16/19)
Citrobacter freundii complex	**77.8%** (14/18)	**75.0%** (9/12)
Proteus mirabilis	**62.5%** (5/8)	**77.8%** (7/9)
Pseudomonas aeruginosa	**85.7%** (30/35)	**94.4%** (34/36)

TOC, test of cure.

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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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.

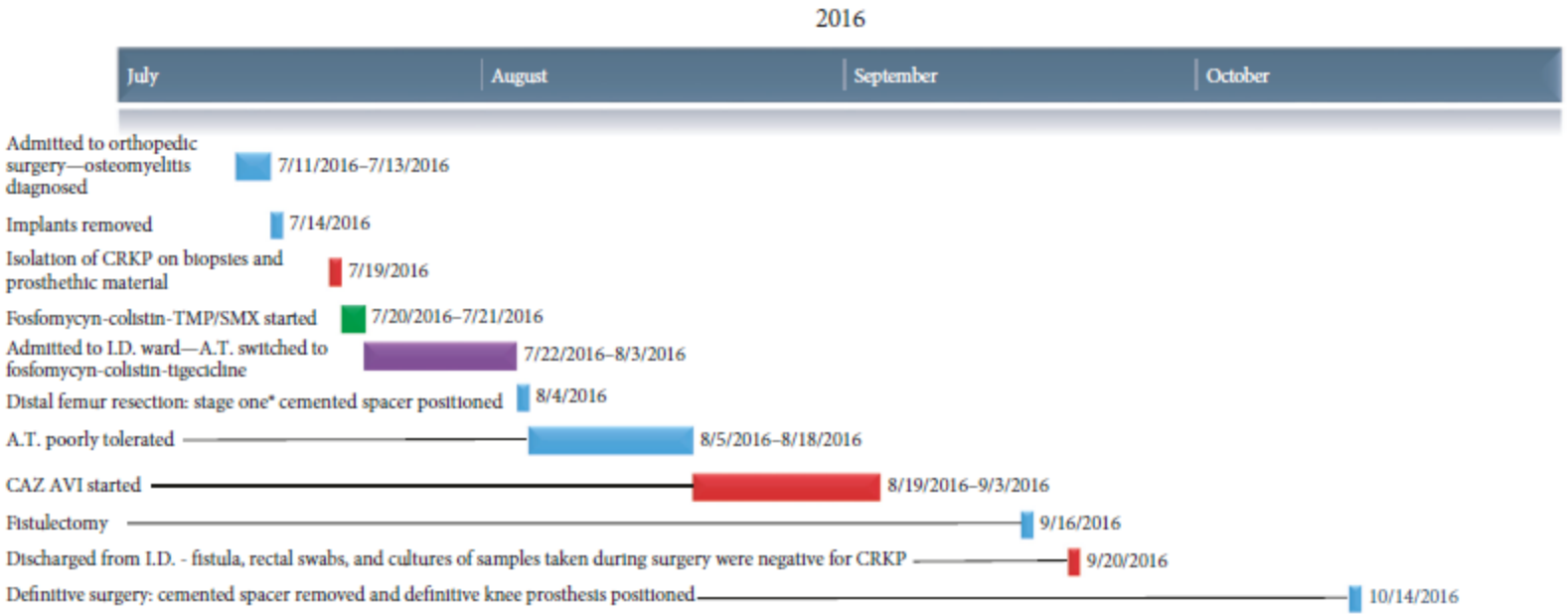

Figure 4: Timeline of antibiotic and surgical treatments.

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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.)

TABLE 3 Summary of ceftazidime and avibactam pharmacokinetic parameters measured in pediatric patients (pharmacokinetic population)

Drug and parameter[a]	Value for cohort: 1 ($n = 8$) (≥12 to <18 yr)	2 ($n = 8$) (≥6 to <12 yr)	3 ($n = 8$) (≥2 to <6 yr)	4 ($n = 8$) (≥3 mo to <2 yr)
Ceftazidime				
C_{max} (mg/liter)	79.8 (41.8)	81.3 (17.8)	80.1[b] (14.7)	91.7[b] (19.6)
t_{max}[c] (h)	2.0 (1.9–2.6)	2.1 (1.9–2.4)		
AUC_{0-t} (h · mg/liter)	229.2 (30.9)	217.8 (18.4)		
$AUC_{0-\infty}$ (h · mg/liter)	230.6 (30.7)	221.2 (17.4)		
$t_{1/2}$[c] (h)	1.7 (0.9–2.8)	1.6 (0.9–1.8)		
V_{ss} (liters)	22.2 (42.0)	13.0 (17.8)		
CL (liter/h)	8.7 (45.5)	5.6 (16.0)		
CL/W (liter/kg/h)	0.169 (37.9)	0.226 (20.0)		
Avibactam				
C_{max} (mg/liter)	15.1 (52.4)	14.1 (23.0)	13.7[b] (22.4)	16.3[b] (22.6)
t_{max} (h)	2.0 (1.9–2.6)	2.1 (1.9–2.4)		
AUC_{0-t} (h · mg/liter)	36.3 (33.7)	34.4 (23.4)		
$AUC_{0-\infty}$ (h · mg/liter)	36.4 (33.6)	34.8 (22.6)		
$t_{1/2}$ (h)	1.6 (0.9–2.8)	1.7 (0.9–2.0)		
V_{ss} (liters)	31.0 (53.3)	19.3 (27.0)		
CL (liter/h)	13.7 (52.6)	8.9 (30.2)		
CL/W (liter/kg/h)	0.267 (44.2)	0.359 (35.8)		

[a] Values are geometric mean (coefficient of variation [%]) unless stated otherwise. CL/W, weighted clearance or clearance by body weight.

[b] Plasma concentration as measured at end of infusion.

[c] Median (range).

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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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