ANG HEALTHCARE

PANORAMA Study: a multinational prospective cohort study demonstrated:

Carbapenem resistance is associated with increased length of hospital stay and mortality in patients with bloodstream infections in countries like India

(Lancet Infect Dis 2019;19(6):601–10)

CEFTAZIDIME-AVIBACTAM appears to be a promising drug for treating CARBAPENEM RESISTANT ENTEROBACTERIACEAE infections, especially those involving bacteremia

(Infection and Drug Resistance 2022:15: 6907-6926)

Colistin Versus Ceftazidime-Avibactam in the Treatment of Bacteremia due to Carbapenem-Resistant Enterobacteriaceae

KEFUZID®-AV
(Ceftazidime 2g + Avibactam 0.5g)

A prospective, multicenter, observational study.

Patients initially treated with either ceftazidime-avibactam or colistin for CRE infections were selected from the Consortium on Resistance Against Carbapenems in Klebsiella and other Enterobacteriaceae **(CRACKLE)**.

Efficacy, safety and Benefit-risk Outcome in the First 30 Days of Treatment

	Ceftazidime-Avibactam First	Colistin First
OUTCOME	**(%)**	**(%)**
EFFICACY		
Disposition (n=137)	n=38	n=99
Hospital death	8%	33%
Alive in hospital or discharged not to home	71%	60%
Discharged home	21%	7%
SAFETY		
Death and incident renal failure (n=72)	n=26	n=46
Hospital death	8%	26%
Not observed to die, with incident renal failure	4%	13%
Not observed to die, without incident renal failure	88%	61%
BENEFIT RISK		
Analysis for death, discharge and incident renal failure (n=72)	n=26	n=46
Hospital death	8%	26%
Alive in hospital or discharged not to home, incident renal failure	4%	11%
Alive in hospital or discharged no to home, no incident renal failure	65%	54%
Discharged home	23%	9%

Conclusions: Ceftazidime-avibactam (KEFUZID-AV) may be a reasonable alternative to colistin in the treatment of K. pneumoniae carbapenemase–producing CRE infections.

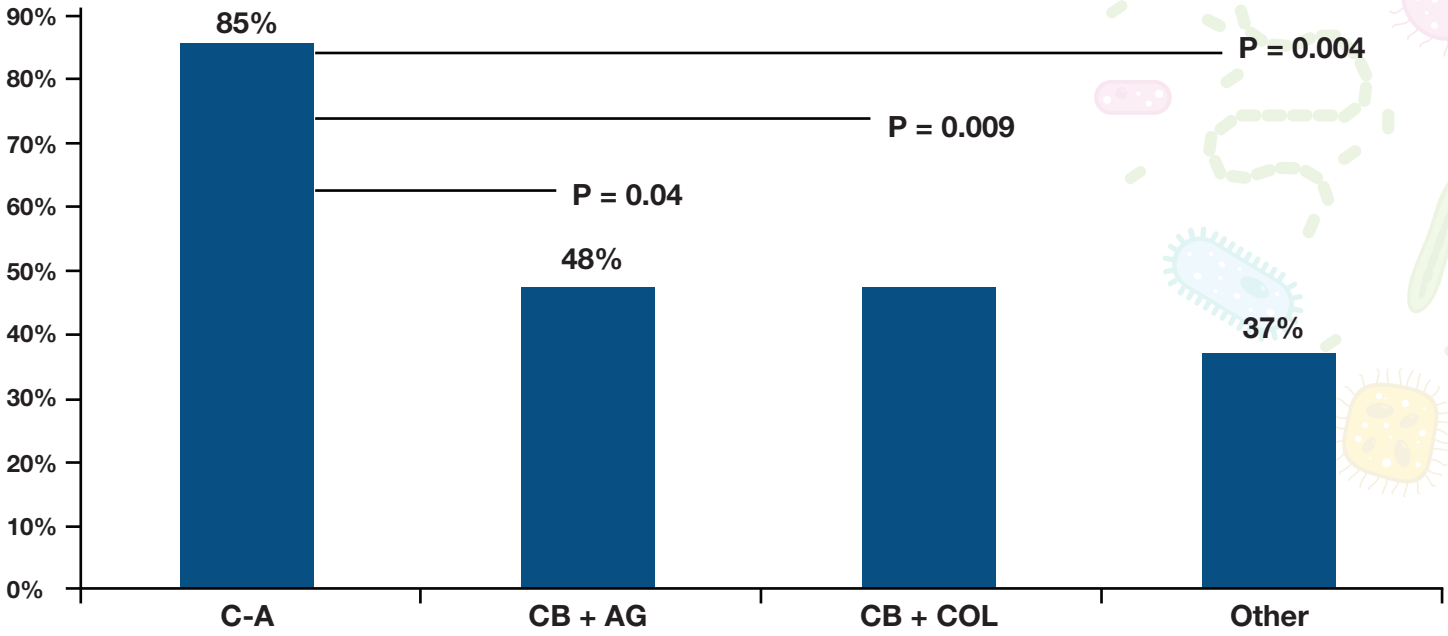
Clinical Infectious Diseases 2018;66(2):163–71

Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant Klebsiella pneumoniae (CR-Kp) Bacteremia

KEFUZID®-AV
(Ceftazidime 2g + Avibactam 0.5g)

Randomized, double-blind study

Objective: To compare the outcomes of patients with carbapenem-resistant K. pneumoniae (CR-Kp) bacteremia who received definitive treatment with a regimen containing Ceftazidime-Avibactam or alternative regimens (carbapenem plus aminoglycoside [CBAG], carbapenem plus colistin [CBCOL], or others [including monotherapy with AG or COL]).



Rates of 30-day clinical success across treatment regimens. Among patients with carbapenem-resistant *Klebsiella pneumoniae* bacteremia, rates of clinical success were significantly higher among patients receiving ceftazidime-avibactam than among those who recevied a carbapenem plus aminoglycoside (p = 0.04) or colistin (P = 0.009) or other regimnes (P = 0.004). Other regimens included aminoglycoside (n = 11), carbapenem (n = 8), colistin (n = 4), tigecycline (n = 4), and ciprofloxacin (n = 2) monotherapy, as well as combination regimens of colistin plus tigecycline (n = 3,) aminoglycoside plus tigecycline (n = 2), and 1 each of aminoglycoside plus cefepime, aminoglycoside plus colistin plus tigecycline, colistin plus aztreonam, colistin plus cefepime, colistin plus ciprofloxacin, carbapenem plus doxycycline, and carbapenem plus tigecycline.

Clinical success and survival were significantly improved for patients with CR-Kp bacteremia who received Ceftazidime-Avibactam (KEFUZID-AV).

Antimicrob Agents Chemother 61:e00883-17. https://doi.org/10.1128/AAC.00883-17.

Safety and efficacy of Ceftazidime/ avibactam plus Metronidazole V/S Meropenem in Complicated intra abdominal infection (cIAI)

KEFUZID®-AV

(Ceftazidime 2g + Avibactam 0.5g)

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)	
		N	Clinical cure n(%)	N	Clinical Cure [n (%)]
All isolates	CAZ-NS	23	22 (95.7)	26	25 (96.2)
	CAZ-S	76	70 (92.1)	89	84 (94.4)
Enterobacteriaceae	CAZ-NS	21	20 (95.2)	25	24 (96.0)
	CAZ-S	70	64 (91.4)	81	78 (96.3)
Escherichia coli	CAZ-NS	14	13 (92.9)	23	22 (95.7)
	CAZ-S	54	50 (92.6)	53	51 (96.2)
Klebsiella pneumoniae	CAZ-NS	3	3 (100)	1	1 (100)
	CAZ-S	16	15 (93.8)	26	25 (96.2)
Non-Enterobacteriaceae	CAZ-NS	2	2 (100)	1	1 (100)
	CAZ-S	15	15 (100)	15	13 (86.7)
Pseudomonas aeruginosa	CAZ-NS	1	1 (100)	0	0
	CAZ-S	10	10 (100)	14	12 (85.7)

Ceftazidime/Avibactam (KEFUZID-AV) plus metronidazole was noninferior to meropenem in the treatment of patients with cIAI in Asian countries, with a safety profile reflective of ceftazidime alone. In addition, combination was effective against ceftazidime-non-susceptible Enterobacteriaceae.

Qin X, Tran BG, KimMJ et al. A randomised, double-blind, phase 3 study comparing the efficacy and safety of ceftazidime/avibactam plusmetronidazole versus meropenemfor complicated intra-abdominal infections in hospitalised adults in Asia. Int J Antimicrob Agents 2017; 49: 579–88.

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

KEFUZID®-AV
(Ceftazidime 2g + Avibactam 0.5g)

Prospective data from 135 centres in 23 countries :

	Patient with clinical cure (clinically evaluable population)		Patient with favorable microbiological response (extended microbiologically evaluable population)	
	Ceftazidime-avibactam (n=257)	Meropenem (n=270)	Ceftazidime-avibactam (n=125)	Meropenem (n=131)
Enterobacteriaceae				
Klebsiella pneumoniae	83.80%	79.60%	78%	79.60%
Enterobacter cloacae	95.20%	63.60%	85.70%	63.60%
Escherichia coli	72.70%	77.80%	90.90%	88.90%
Proteus mirobilis	100%	87.50%	82%	75%
Serratia marcescens	83.30%	100%	75.00%	62.50%
Enterobacter aerogenes	66.70%	40%	83.30%	60%
Gram- negative pathogen other than Enterobacteriaceae				
Pseudomonas aeruginosa	64.30%	77.10%	42.95%	40%
Haemophilus influenzae	90.00%	84.60%	100%	92.30%
Gram- Positive aerobes				
Staphylococcus aureus	78.60%	72.70%		

Per-pathogen clinical cure rates and favorable microbiological response rates at test-of-cure visit.

Ceftazidime-Avibactam (KEFUZID-AV) was non-inferior to meropenem in the treatment of nosocomial pneumonia. These results support a role for Ceftazidime-Avibactam as a potential alternative to carbapenems in patients with nosocomial pneumonia (including ventilator-associated pneumonia) caused by Gram-negative pathogens.

Torres A, Zhong N, Pachl J et al. Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial. Lancet Infect Dis 2018; 18: 285–95.

Comparative study of ceftazidime/ avibactam plus metronidazole versus meropenem in the treatment of cIAI in hospitalized adults:

KEFUZID®-AV

(Ceftazidime 2g + Avibactam 0.5g)

Results of a randomized, double-blind, Phase II trial performed in accordance with International Conference on Harmonization/Good Clinical Practice guidelines in 204 Patients.

Favorable clinical response at the TOC visit in Patients according to baseline APACHE-II score and primary site of infection (ME population)

	Ceftazidime/ avibactam and metronidazole (n=68)	Meropenem (n=76)
APACHE II score		
0 to 5	94.30%	92.90%
6 to 10	81%	91.30%
11 to 15	100%	100%
16 to 19	10%	0%
Primary Infection Site		
stomach/duodenum	89%	100%
gall bladder	66.70%	100%
appendix	93.80%	91.90%
small bowel	100%	90%
colon	88.90%	80%
liver/spleen/other	100%	100%

Result are expressed as number of patients with favorable clinical response/total number of patient in each category (%)

Favourable microbiological response overall and according to pathogen isolated from the intra-abdominal site at the TOC visit (ME population)

Pathogen	Ceftazidime/ avibactam and metronidazole (n=68)	Meropenem (n=76)
Overall	**91.20%**	**93.45**
Gram-positive aerobe		
Enterococcus faecium	75%	100%
other	100%	100%
Gram-negative aerobe		
Escherichia coli	90%	93%
Klebsiella pneumoniae	100%	100%
Klebsiella aeruginosa	100%	100%
Klebsiella oxytoca	100%	100%
Acinetobacter baumanni	100%	100%
Enterobacter aerogenes	0%	0%
Enterobacter cloacae	100%	100%
Other	100%	100%
Anaerobe		
Bacteroides fragilis	50%	100%
Other	100%	100%

Ceftazidime/avibactam (KEFUZID-AV) plus metronidazole was effective and generally well tolerated in patients with cIAI, with a favourable clinical response rate in the ME population of >90%, similar to that of meropenem.

Lucasti C, Popescu I, Ramesh MK et al. Comparative study of the efficacy and safety of ceftazidime/avibactamplus metronidazole versusmeropenem in the treatment of complicated intra-abdominal infections in hospitalized adults: results of a randomized, double-blind, Phase II trial. J Antimicrob Chemother 2013; 68: 1183–92.

Efficacy and Safety of Ceftazidime-Avibactam Plus Metronidazole Versus Meropenem in the Treatment of Complicated Intra-abdominal Infection: Results From a Randomized, Controlled, Double-Blind, Phase 3 Program

KEFUZID®-AV

(Ceftazidime 2g + Avibactam 0.5g)

Prospective, multi centre data from Tow Global Studies (Reclaim - 1 & Reclaim - 2) : 1006 Patients

Clinical Cure Rate at Test-of-cure Visit (Primary End Point) and End-of-Treatment and late-follow-up visits (secondary End points) for Patients in the Microbiologically Modified Intention to Treat and Clinically Evaluable at Test-of-cure Visit Analysis Populations.

	mMITT		MITT		CE at TOC	
End Points	**Ceftazidime-Avibactam + Metronidazole (n=413)**	**Meropenem (n=410)**	**Ceftazidime-Avibactam + Metronidazole (n=413)**	**Meropenem (n=410)**	**Ceftazidime-Avibactam + Metronidazole (n=413)**	**Meropenem (n=410)**
Primary						
Cure at TOC	81%	85.10%	82.50%	84.90%	91.70%	92.50%
Secondary						
Cure at EOT, No (%)	87%	92.40%	88.30%	92.20%	92.90%	95.20%
Cure at LFU visit	82%	84.60%	82.60%	83.40%	90%	90.40%

Conclusions:

Ceftazidime-avibactam (KEFUZID-AV) plus metronidazole was no inferior to meropenem in the treatment of complicated intraabdominal infections.

Efficacy was similar against infections caused by ceftazidime-susceptible and ceftazidime-resistant pathogens.

Abbreviations: CE, Clinically Evaluable; CI, Confidence Interval; EOT, End-of-treatment; LFU, Late-follow-up; MITT, Modified Intention-to-treat; mMITT, Micro-biologically MITT; TOC, Test-of-cure.

Mazuski JE, Gasink LB, Armstrong J et al. Efficacy and safety of ceftazidime-avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infection: results from a randomized, controlled, double-blind, phase 3 program. Clin Infect Dis 2016; 62: 1380–9.

For serious and difficult-to-treat infections

KEFUZID®-AV

(Ceftazidime 2g + Avibactam 0.5g)

FDA Approved indications - cUTI, cIAI, HABP and VABP

Approved by US FDA for pediatric patients 3 months and older for the treatment of complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI) in combination with metronidazole.

EMA Approved indication – Authorised for the Treatment of Complicated Intra-Abdominal Infections, Complicated Urinary Track Infections, including Pyelonephritis, Hospital-Acquired Pneumonia including Ventilator-Associated Pneumonia, and for the treatment of infections due to aerobic Gram-negative organisms in adult Patients with limited treatment options.

Type of infection	Dose of ceftazidime/avibactam	Frequency	Infusion time	Duration of treatment
cIAI[2,3]	2 g/0.5 g	Every 8 hours	2 hours	5-14 days
cUTI, including pyelonephritis[3]				5-10 days
HAP/VAP[3]				7-14 days
Bacteraemia associated with, or suspected to be associated with any of the above infections				Duration of treatment should be in accordance with the site of infection.

No Dosage adjustment is required in patients with mild renal impairment (estimated CrCl[1] 51 to < 80ml/min) and those with hepatic impairment

*Antimicrob Agents Chemother 2017;61(8).

Abbreviation:
(**cIAI:** Complicated intra abdominal infection, **cUTI:** complicated Intra abdominal infections, **HABP:** Hospital Acquired Bacterial Pneumoniae and **VABP:** Ventilator Associated Bacterial Pneumoniae)

1. CrCl estimated using the Cockcroft-Gault formula.
2. To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process.
3. To be used in combination with an antibacterial agent active against Gram-positive pathogens when these are known or suspected to be contributing to the infectious process.

ANG LIFESCIENCES INDIA LTD.

(More than a decade of Trust)

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