Ceftazidime-avibactam as a real-world treatment option for infections caused by Carbapenem-Resistant Gram-negative bacilli

Molina-Jaimes Aaron, Olmedo-Reneaum Alejandro, Martínez-Toledo Angela A, González-Ayala Marcelino, García-Araiza Mayra G, Sanabria-Trujillo Giovanni, Molina Mariana

Background

Multidrug-resistant Gram- negative bacilli (MDR GNB) infections are associated with important morbidity and mortality in hospitalized patients worldwide. One of the greatest concerns regarding Carbapenem-Resistant Gram-negative bacilli (CR GNB) infections is the increasing incidence in the last 20 years; making these infections a major public health threat. The Centers for Disease Control and Prevention (CDC) recommends taking crucial actions against these infections. This issue is of great concern to the Latin American region where carbapenem resistance has been documented in Enterobacterales (formerly Enterobacteriaceae) and *Pseudomonas aeruginosa*. In Mexico, carbapenem-resistant Enterobacterales have a prevalence between 3-4%, and for *Pseudomonas aeruginosa* can be as high as 20%. The aim of this study is to report real-world-evidence of the use of ceftazidime-avibactam against CR GNB infections (Enterobacterales and *Pseudomonas aeruginosa*) in Mexico.

Methods

- We included all infections caused by CR GNB isolates identified in the time period, infections were independently reviewed and classified in light of the available clinical, laboratory, and radiographical data by the infectious disease specialists in charge (two in one center and one in the other), following international guidelines.
- All patients received a standardized dose of 2.5 gr of Ceftazidime-avibactam in a 2 hour infusion period regardless of renal function.
- Identification and susceptibility of microorganisms were determined with Vitek2 system and CLSI cut-off points 2019.
- When it was available GeneXpert® Carba-R (Cepheid) was used for detection of bla $_{KPC}$, bla $_{NDM}$, bla $_{IMP}$, bla $_{VIM}$, and bla $_{OXA-48}$.
- Main clinical outcomes were clinical and microbiological cure.

Results

79 cases of infections caused by CR GNB were analyzed. Distribution of infectious syndromes was: 40% urinary tract infections (UTI), 18% healthcare associated pneumonia (HCAP), 17% bacteremia, 15% post-surgical infections, and 9% skin and soft tissue infections (SSTI). Clinical cure was accomplished in all bacteremia cases, HCAP and SSTI, in 87.5% of UTI, and in 91.6% of post-surgical infections. Microbiological cure was reported in all bacteremia cases, 92% of UTI, and 72.7% of HCAP.

Bibliography

1.- Centers for Disease Control and Prevention (U.S.). Antibiotic resistance threats in the United States, 2019 [Internet]. Centers for Disease Control and Prevention (U.S.); 2019 Nov [cited 2021 Dec 5]. Available from: https://stacks.cdc.gov/view/cdc/82532
2.- García-Betancur JC, Appel TM, Esparza G, Gales AC, Levy-Hara G, Cornistein W, et al. Update on the epidemiology of carbapenemases in Latin America and the Caribbean. Expert Rev Anti Infect Ther [Internet]. 2021 Feb 1 [cited 2021 Dec 5];19(2):197–213. Available from: https://www.tandfonline.com/doi/full/10.1080/14787210.2020.1813023
3.- Garza-González E, Franco-Cendejas R, Morfín-Otero R, Echaniz-Aviles G, Rojas-Larios F, Bocanegra-Ibarias P, et al. The Evolution of Antimicrobial Resistance in Mexico During the Last Decade: Results from the INVIFAR Group. Microb Drug Resist [Internet]. 2020 Nov 1 [cited 2021 Dec 5];26(11):1372–82. Available from: https://www.liebertpub.com/doi/10.1089/mdr.2019.0354
4.- Das S, Li J, Riccobene T, Carrothers TJ, Newell P, Melnick D, et al. Dose Selection and Validation for Ceftazidime-Avibactam in Adults with Complicated Intra-abdominal Infections, Complicated Urinary Tract Infections, and Nosocomial Pneumonia. Antimicrob Agents Chemother [Internet]. 2019 Apr [cited 2021 Dec 5];63(4). Available from: https://journals.asm.org/doi/10.1128/AAC.02187-18

Table I. Distribution of microorganisms by infectious site.

Type of infection	Microorganism (%)				
	Klebsiella pneumoniae	*Klebsiella oxytoca*	*Pseudomonas aeruginosa*	*Enterobacter cloacae*	*Escherichia coli*
Urinary tract infection* (N= 32)	37.5	3.1	34.3	9.3	15.6
Health care associated pneumonia (N=14)	35	0	50	0	14.2
Primary bacteremia (N=14)	57.1	7	7	21.4	7
Organ/space Post-surgical infections (N=12)	8.3	8.3	50	8.3	25
Skin and soft tissue infection(N= 7)	42.8	0	42.8	0	14.2

Table II. Analysis of documented antimicrobial resistance of CR GNB isolates.

Microorganism	Antimicrobial (% resistance)						
	Meropenem	Piperacillin-tazobactam	Cefepime	Levofloxacin	Tigecycline	Amikacin	CR identified causes (% of isolates)
Klebsiella pneumoniae N=29	100	100	100	90	27.6	37.9	bla$_{KPC}$ (14%) ESBL+AmpC (41%)
Klebsiella oxytoca N=3	100	100	100	66.6	66.6	100	blaKPC (66%)
Pseudomonas aeruginosa N=28	99	82.4	78.5	92		40	Not documented
Enterobacter cloacae N=7	98	71.4	90.8	85.7	28.5	14.28	Not documented
Escherichia coli N=12	99	91.6	100	100	34.4	25	bla$_{KPC}$ (16%), ESBL+ AmpC c (50%)

Table III. Comparison of biochemical parameters in patients receiving ceftazidime-avibactam as monotherapy compared to combination therapy. Before and after treatment.

Biochemical parameters	Before			After		
	Monotherapy (n=54)	Combination therapy (n=25)	P-value	Monotherapy(n=54)	Combination therapy(n=25)	P-value
Total leukocytes (per µL)	12.04 (1.78-26.8)	12 (3.4-28.6)	0.935	6.5 (2.0-13-69)	7.1 (2.3-13.6)	0.098
Total neutrophiles (per µL)	9.6 (1.6-26.39)	10.5 (2.6-23.5)	0.973	4.5 (1.69-12-3)	5.06 (1.07-12.3)	0.273
Hemoglobin (g/dL)	10.3 (86.9-13.6)	10 (7.5-14.6)	0.987	10.6 (7.2-13.8)	10.2 (8.2-14.0)	0.045
Platelets (per µL)	226 (48-565)	242 (48-612)	0.7	267 (74-479)	240 (74-373)	0.497
Creatinine (mg/dL)	1.2 (0.3-3.8)	1.6 (0.3-4.1)	0.026	1.5 (0.5-2.3)	1.3 (1-3.2)	0.868
GFR (ml/min/1.73m^2)	71 (17-156)	62.5 (15-12.4.2)	0.388	78 (15-160)	72 (12.5-129)	0.087
C reactive protein (mg/dL)	116 (5-214)	79 (5-214)	0.457	15 (0.5-55)	18.8 (0.5-51)	0.703

Conclusion

Our study supports the use of ceftazidime-avibactam for infections caused by CR GNB. Studies with a larger population are needed in our country to be able to generalize these results.