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Letter to the Editor

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Nosocomial meningitis caused by ESBL- and OXA-48-producing *Klebsiella pneumoniae* and treated with ceftazidime-avibactam. Report of one case and review of the literature

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Sir,

The infections caused by carbapenemase-producing *Klebsiella pneumoniae* (CPKP) have limited treatment options, [1-3]; this implies an even worse problem if the infection is located in the central nervous system (CNS), due to the limited blood-brain barrier (BBB) penetration of the antibiotics and, therefore, the need for higher doses. There is scarce evidence regarding the optimal dose and the cerebrospinal fluid (CSF) concentration of most new antibiotics used for the treatment of CPKP, including OXA-48-producing *K. pneumoniae*.

CAZ-AVI is a new beta-lactam combined with extended-spectrum beta-lactamase (ESBL) inhibitor against Gram-negative bacilli (GNB), both fermenters and non-fermenters [2,4], whose action spectrum include Ambler class A (KPC), class D (OXA-48), and many class C (Amp-C) CPKP [5-9]. Thus, it constitutes the first therapeutic option in CPKP-triggered infections that are not located in the urinary tract [10].

We report the case of a patient with nosocomial meningitis caused by ESBL- (CTX-M-15) and OXA-48-producing *K. pneumoniae* related to an external lumbar drainage (ELD) that was successfully treated intravenous CAZ-AVI in combination with intrathecal amikacin. In addition, we also perform a review of the literature of CPKP-triggered nosocomial meningitis.

Our patient was a 50-year-old male who was admitted to our hospital due to a craniocerebral trauma (CCT). A CT-scan was performed and showed multiple skull fractures, bilateral subdural hematoma, generalized subarachnoid hemorrhage, frontal lobe seizures, and cerebral edema. He required an urgent neurosurgery with a decompressive craniectomy, fracture repair, and edema removal. After the surgery, he was admitted to the Intensive Care Unit (ICU).

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During his stay in the ICU, he underwent a rectal culture that resulted positive for ESBL- and OXA-48-producing *K. pneumoniae*, which was isolated in selective chromogenic media (CHROMID ESBL and CHROMID CARBA SMART (bioMérieux)). Consequently, the appropriate isolation measures were implemented. Afterwards, the patient developed a mechanical ventilation-associated pneumonia due to such pathogen and, therefore, treatment with CAZ-AVI was decided.

At the 20th day of admission, the patient was moved to the neurosurgery ward in a situation of unresponsive wakefulness syndrome with a percutaneous tracheostomy. Nine days after, an ELD was required as a consequence of cognitive impairment. It was not possible to perform an external ventricular drainage (EVD) due to the lack of bone support at the cranial vault.

At the 39th day of admission, he developed a severe sepsis without any other apparent focal point of infection. Blood and CSF samples were obtained for culture, and treatment with meropenem, in expanded perfusion, and vancomycin was started. The CSF culture showed biochemical and cytological results consistent with bacterial meningitis (Leukocytes 1016 leuk/ul, 75% PMN, GLU 41 mg/dl, (blood glucose 93 mg/dl) proteins 129.3mg/dl, lactate 5.4 mmol/L). An ESBL- and OXA-48-producing *K. pneumoniae* was isolated, using mass spectrometry for the identification (MALDI Biotyper system®, Bruker Daltonics, Germany), and fast colorimetric (β-lactatest®, BIO-RAD y β-carbatest®, BIO-RAD); in addition, immunochromatographic (NG-Test CARBA5®, NG-BIOTECH) assays were employed for the evaluation of the susceptibility and mechanisms of resistance. The ESBL- (CTX-M-15) and OXA-48-producing *K. pneumoniae* was resistant to meropenem (MIC > 8 mg/L) and susceptible to CAZ-AVI, with a MIC of 0.5 mg/L (Vitek2 bioMérieux) [11].

Thus, CAZ-AVI treatment was decided and doses were optimized, increasing the frequency of administration to 2/0.5g every 6 hours, and intrathecal amikacin was added (following our hospital recommendations) during 21 days. After 48 hours

of treatment, the ELD shunt was changed and CSF cultures were repeated: at the moment the shunt was changed, 3 days after, and then every 5 days, with all of them giving negative results.

The hospital stay was long, there were no changes in the patient's status and, at the day +150, he was discharged to a long-stay hospital.

Globally, nosocomial infections have a high prevalence in patients who have undergone a craniectomy. Indeed, up to 40% of these patients suffer a nosocomial infection, with mechanical ventilation-associated pneumonia being the most common one (it accounts for 22% of cases). Drainage (both EVD and ELD) constitutes one of the most important risk factors for developing nosocomial meningitis, with an estimated prevalence of 5-16% for EVD and 7% for ELD.

Traditionally, the pathogens most frequently involved in nosocomial meningitis associated with drainage were Gram-positive bacteria, mainly *Staphylococcus* spp. However, over recent years there has been an increase in GNB, including multi-resistant GNB [12-14].

The BBB penetration of the antibiotics towards the CSF is poorly-defined or unknown, and many antibiotics cannot be used at the systemic doses that would be necessary due to the associated toxicity. Therefore, the combination of systemic and intrathecal treatments is frequent, especially in case of multi-resistant bacteria [15].

When ceftazidime is administered parenterally, it reaches a good concentration (as it occurs generally with all beta-lactams): above the minimal inhibitory concentration in CSF. However, its intrathecal administration is not recommended due to neurotoxicity, mainly because it can favor epileptic seizures. The optimal dose for the CNS is 2g in intervals of 6 or 8 h [14].

The IDSA Clinical Practice Guidelines state that, although the intrathecal use of antimicrobials is not approved by the FDA, it has to be considered as an option for nosocomial meningitis/ventriculitis that do not respond to systemic treatment. Aminoglycosides such as amikacin have a good safety profile, as well as better pharmacokinetic/pharmacodynamic (PK/PD) properties and effectiveness, compared to when they are administered systemically [16].

CAZ-AVI is a novel combination of beta-lactam + beta-lactamase inhibitor that has been approved by the FDA and EMA for intraabdominal and urinary tract infections, as well as for mechanical ventilation-associated pneumonia and in cases of multi-resistant *Enterobacteriaceae* and *Pseudomonas* [17-22].

Data on the use of CAZ-AVI in CSF infections are still scarce, but it has emerged as a therapeutic option in CNS infections caused by CPKP due to its BBB penetration, which has been shown in animal models to be 38% [11], and to its PK/PD properties; as almost 90% of the protein non-bound free fraction of avibactam is responsible for its pharmacodynamic effect [23].

In our study, we report the results of using CAZ-AVI in nosocomial meningitis and review the literature about CSF-drainage-associated meningitis due to CPKP and their treatment with CAZ-AVI. For that purpose, we used PubMed, Mesh, and Cochrane as search engines, and nosocomial meningitis, ceftazidime-avibactam, central nervous system infection; as well as EVD- and ELD-associated meningitis, as terms.

We included all reported cases and case series of CNS infections due to CPKP. We found a total of 11 original papers (9 clinical cases and 2 case series reporting episodes of CNS infections caused by CPKP) published between 2016 and 2021. Among them, 8 received treatment with CAZ-AVI and only one described that the infection was caused by ESBL- and OXA-48-producing *K. pneumoniae*. The characteristics of all cases are shown in Table 1.

In 2016, Mermer *et al.* described the first case of meningitis due to CPKP and associated with ventriculo-peritoneal drainage (VPD). It was successfully treated with polymyxin and changing the shunt [24]. Other authors have reported cases of postsurgical meningitis due to carbapenem-resistant *Enterobacteriaceae* (CRE) that have been successfully treated combining tigecycline or polymyxin with intrathecal amikacin or colistin [25-26].

Evidence regarding the treatment of nosocomial meningitis with CAZ-AVI is still limited; however, it seems to show good results as monotherapy and/or combined therapy in infections induced by CRE *P. aeruginosa* [27-29]. Regarding the retrospective case series, Shields *et al.* and Temkin *et al.* reported 37 and 38 cases (respectively) of CPKP infections that were treated with CAZ-AVI, with 76% and 73% of cure (respectively). Each one of these authors also included a case of ventriculitis due to CPKP [8,30].

Samuel *et al.* described for the first time a case of nosocomial meningitis due to KPC treated with CAZ-AVI every 6 hours during 14 days. This case, which resulted in clinical and microbiological cure [31], constitutes the unique reported case, apart from ours, in which an increase in CAZ-AVI frequency of administration from 8 to 6 hours has been performed.

Notwithstanding, Yasmin *et al.* [32] also published a case of KPC meningitis treated with standard doses of CAZ-AVI, every 8 hours during 14 days, and intrathecal amikacin. They evaluated CAZ-AVI levels in CSF and confirmed that the usual dose of 2g/0.5g every 8 hours achieved an adequate concentration.

Treatment duration in these infections is still under discussion. The IDSA guidelines recommend that treatments should last 10-14 days in meningitis caused by GNB, although some experts recommend 21 days [16]. Nonetheless, there are no recommendations neither on CPKP nor on OXA-48. However, the literature shows great variabilities regarding treatment duration, with good results being reported for treatments lasting 14 days, 21 days, and even more than 6 weeks [27,28,30,31] and treatment options are discussed. Summary. Few antibiotics to treat carbapenem-resistant Enterobacteriaceae (CRE. We decided to prescribe a 21-day treatment, which was effective to cure the infection

Table 1 **Main characteristics of the cases reported in the literature.**

Author, year [reference]	Material and methods	Microbiological isolation	Previous treatment	Systemic treatment, dose and duration	Intrathecal treatment	Evolution
Mermer S, 2016 [24]	1 case (infarction and VPD)	CPE *K. pneumoniae*	Not available	IV colistin	Colistin	Not available
Samuel S, 2016 [31]	1 case of nosocomial meningitis after a hemicraniectomy. No CSF drainage	KPC *K. pneumoniae*	No	CAZ-AVI 2g/0.5g/6h, 14 days	No	Clinical and microbiological cure
Shield R 2016 [30]	Retrospective series of 37 cases treated with CAZ-AVI. One case of ventriculitis and subdural empyema	KPC *K. pneumoniae* (84%) *E. coli* (8%) *E. clocace* (5%) *E. aerogenes* (3%)	No	CAZ-AVI 2g/0.5g/8h, 14 days (mean)	Colistin	30-day survival of 76%, 90-day survival of 69%, not specified for the CNS infection
Temkin E, 2017 [8]	Series of 38 cases: one case of ventriculitis/subdural abscess	*K. pneumoniae* 34: 12 OXA 48 *K. oxytoca* (1) OXA-48 *E coli* (1) *P aeruginosa* (2)	Colistin, tigecycline, carbapenems	CAZ-AVI 2g/0.5g/8h, 16 days (mean)	Not available	Clinical and microbiological cure of 73.7% of the series, not specified for the CNS infection
Gofman N, 2018 [27]	1 case, CCT, craniectomy, EVD, VPD +10 sepsis +30 VPD	*Carbapenemase K. pneumoniae* and *P. aeruginosa*	Vancomycin, ceftriaxone, cefepime, meropenem	CAZ-AVI 2g/0.5g/8h, 6 weeks	Amikacin 30mg, 4 weeks	Clinical and microbiological cure
Holyk A, 2018 [28]	1 case, elderly, subarachnoid hemorrhage, EVD, UIP day +23, CNS infect. +31	*Carbapenemase K. pneumoniae* (MIC meropenem>8)	Cefazolin, piperacillin tazobactam, CAZ-AVI, inhaled colistin, doxycycline	CAZ-AVI 2g/0-5g/8h, 21 days	Gentamicin, 15 days	Clinical and microbiological cure
Dacco V, 2019 [29]	1 case, multiple brain abscesses and bacteremia after lung transplantation, due to Burkholderia multivorans	PenA Class A *B. multivorans carbapenemase*	Meropenem, trimethoprim, sulfamethoxazole, levofloxacin	CAZ-AVI 2g/0.5g/ added post-hemodialysis, 102 days	No	Clinical and microbiological cure
Chen Y, 2019 [25]	1 case of meningitis with brain abscess after surgery, 29-year-old male. EVD	KPC *K. pneumoniae*	No	Tigecycline + IV amikacin, 23 days and TMP-SMX + oral minocycline, 32 days	Amikacin	Clinical and microbiological cure
Patrial Y, 2019 [26]	Case 1: 17-year-old male, CCT, EVD + decompressive craniectomy. Meningitis day +11 Case 2: 50-year-old female, CCT after subarachnoid hemorrhage, EVD. Meningitis day +16	KPC *K. pneumoniae* KPC *K. pneumoniae*	Case 1: Meropenem Case 2: Piperacillin tazobactam 4.5g/6h, 7 days, Linezolid 600mg/12h, 10 days	C1: polymyxin E 150mg/12h +Meropenem 2g/8h, 19 days C2: polymyxin E 150mg/12h, 7days +Meropenem 1g/8h	Polymyxin E 5mg/24h, 7 days Polymyxin E 5mg/24h, 7 days	Clinical and microbiological cure
Yasmin M, 2020 [32]	1 case, CCT, intrathecal pump. Pump removal. Sepsis with blood culture,CSF and ASB. CAZ-AVI blood and CSF levels were evaluated 184 min after administration: 19/4 in CSF and 61/13 in blood.	KPC-3 *K. pneumoniae*	Meropenem, vancomycin, meropenem vaborbactam, ciprofloxacin	CAZ-AVI 2g/0.5g/8h, 14 days	Amikacin 30mg, 14 days	Yes; CSF/plasma levels confirmed adequate concentration reached through usual dose 2,5g/8h * CAZ-AVI mouse concentration, BBB penetration of 40%
Pektezel M.Y, 2021 [33]	1 case, 62-year-old male, cerebellar hematoma with EVD, day +18 bacteremia due to CPE K pneumonia. Meningitis day +24 and brain abscess	OXA-48 *K. pneumoniae*	Meropenem, colistin, ertapenem, fosfomycin	Meropenem 2g/8h, 45 days CAZ-AVI 2g/0.5g/8h, 30 days + TMP-SMX, 15 days	Colistimethate sodium 10mg, 36 days Amikacin 15mg, from day +45	Clinical and microbiological cure

On another front, whether the use of CAZ-AVI for the treatment of CNS infections should be done as monotherapy or in combination with an intrathecally administered drug is also controversial. In the literature, it is frequently combined with intrathecal gentamicin, amikacin, or colistin, although good results have also been reported for CAZ-AVI as monotherapy [29-33].

In spite of the systematic use of CAZ-AVI as combined therapy not being recommended, there are no studies demonstrating that CAZ-AVI displays a worse performance in monotherapy, compared to a combined therapy. Thus, as our patient with nosocomial meningitis caused by ESBL- and OXA-48-producing *K. pneumoniae* had already received a previous treatment with CAZ-AVI (which could predispose towards treatment failure), we decided to use CAZ-AVI in combination with intrathecal amikacin, with good results [10]

As far as we are concerned, we report the second case of meningitis associated with external drainage due to ESBL- and OXA-48-producing *K. pneumoniae* successfully treated 2 g/0.5g/6h of CAZ-AVI and intrathecal amikacin.

In spite of more studies being required, CAZ-AVI has been shown to be a safe, effective, and well-tolerated treatment for CNS infections due to CPKP, either mono- or poly-microbial. Its PK/PD properties allow it penetrate the BBB and reach an adequate concentration in the CSF. CAZ-AVI in combination with intrathecal aminoglycosides seems to be a good option in cases of meningitis associated with drainage. Thus, CAZ-AVI stands as the first alternative for systemic treatment of CPKP-triggered nosocomial meningitis (a pathology whose incidence is increasing), being the first option for KPC- and OXA-48-producing CPKP.

CONFLICTS OF INTEREST

All authors declare no conflict of interest.

REFERENCES

1 Balkan II, Aygün G, Aydın S, et al. Blood stream infections due to OXA-48-like carbapenemase-producing Enterobacteriaceae: treatment and survival. Int J Infect Dis. 2014;26:51-56. doi:10.1016/j.ijid.2014.05.012

2 Rodríguez-Baño J, Gutiérrez-Gutiérrez B, Machuca I, Pascual A. Treatment of Infections Caused by Extended-Spectrum-Beta-Lactamase-, AmpC-, and Carbapenemase-Producing Enterobacteriaceae. Clin Microbiol Rev. 2018;31(2):e00079-17. doi:10.1128/CMR.00079-17

3 Vena A, Giacobbe DR, Castaldo N, et al. Clinical Experience with Ceftazidime-Avibactam for the Treatment of Infections due to Multidrug-Resistant Gram-Negative Bacteria Other than Carbapenem-Resistant *Enterobacterales*. Antibiotics (Basel). 2020;9(2):71. doi:10.3390/antibiotics9020071

4 AEMPS, "Informe de Posicionamiento Terapéutico de ceftazidima/avibactam (Zavicefta ®)," pp. 1–11, 2018.

5 Wilson GM, Fitzpatrick M, Walding K, et al. Meta-analysis of Clinical Outcomes Using Ceftazidime/Avibactam, Ceftolozane/Tazobactam, and Meropenem/Vaborbactam for the Treatment of Multidrug-Resistant Gram-Negative Infections. Open Forum Infect Dis. 2021;8(2):ofaa651. doi:10.1093/ofid/ofaa651

6 Falcone M, Paterson D. Spotlight on ceftazidime/avibactam: a new option for MDR Gram-negative infections. J Antimicrob Chemother. 2016;71(10):2713-2722. doi:10.1093/jac/dkw239

7 Bassetti M, Vena A, Sepulcri C, Giacobbe DR, Peghin M. Treatment of Bloodstream Infections Due to Gram-Negative Bacteria with Difficult-to-Treat Resistance. Antibiotics (Basel). 2020;9(9):632. doi:10.3390/antibiotics9090632

8 Temkin E, Torre-Cisneros J, Beovic B, et al. Ceftazidime-Avibactam as Salvage Therapy for Infections Caused by Carbapenem-Resistant Organisms. Antimicrob Agents Chemother. 2017;61(2):e01964-16. doi:10.1128/AAC.01964-16

9 Karaiskos I, Lagou S, Pontikis K, Rapti V, Poulakou G. The "Old" and the "New" Antibiotics for MDR Gram-Negative Pathogens: For Whom, When, and How. Front Public Health. 2019;7:151. doi:10.3389/fpubh.2019.00151

10 Tamma PD, Aitken SL, Bonomo RA,et al. Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTR-P. aeruginosa). Clin Infect Dis. 2022;ciac268. doi:10.1093/cid/ciac268

11 Lagacé-Wiens P, Walkty A, Karlowsky JA. Ceftazidime-avibactam: an evidence-based review of its pharmacology and potential use in the treatment of Gram-negative bacterial infections. Core Evid. 2014;9:13-25. Published 2014 Jan 24. doi:10.2147/CE.S40698

12 Hussein K, Rabino G, Feder O, et al. Risk factors for meningitis in neurosurgical patients with cerebrospinal fluid drains: prospective observational cohort study. Acta Neurochir (Wien). 2019;161(3):517-524. doi:10.1007/s00701-019-03801-y

13 Kourbeti IS, Vakis AF, Ziakas P, et al. Infections in patients undergoing craniotomy: risk factors associated with post-craniotomy meningitis. J Neurosurg. 2015;122(5):1113-1119. doi:10.3171/2014.8.JNS132557

14 Jiménez-Mejías ME, García-Cabrera E. Infecciones relacionadas con los sistemas de drenaje de líquido cefalorraquídeo [Infection of cerebrospinal fluid shunt systems]. Enferm Infecc Microbiol Clin. 2008;26(4):240-251. doi:10.1016/s0213-005x(08)72696-x

15 Nau R, Blei C, Eiffert H. Intrathecal Antibacterial and Antifungal Therapies. Clin Microbiol Rev. 2020;33(3):e00190-19.doi:10.1128/CMR.00190-19

16 Tunkel AR, Hasbun R, Bhimraj A, et al. 2017 Infectious Diseases Society of America's Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis. Clin Infect Dis. 2017;64(6):e34-e65. doi:10.1093/cid/ciw861

17 European Medicines Agency.General information about Zaviceta and why its use is authorized in the EU.vol. 44, no. 0, pp. 0–2, 2018.

18 Centre of Drug Evaluation and Research, Available at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugIn-

novation/UCM485053.pdf. Nov. Drugs Summ. -2015, no. January, p. 3, 2016.

19 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(11):1380-1389. doi:10.1093/cid/ciw133

20 Wagenlehner FM, Sobel JD, Newell P, et al. Ceftazidime-avibactam Versus Doripenem for the Treatment of Complicated Urinary Tract Infections, Including Acute Pyelonephritis: RECAPTURE, a Phase 3 Randomized Trial Program. Clin Infect Dis. 2016;63(6):754-762. doi:10.1093/cid/ciw378

21 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(3):285-295. doi:10.1016/S1473-3099(17)30747-8

22 Carmeli Y, Armstrong J, Laud PJ, et al. 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. Lancet Infect Dis. 2016;16(6):661-673. doi:10.1016/S1473-3099(16)30004-4

23 Giri P, Patel H, Srinivas NR. Review of Clinical Pharmacokinetics of Avibactam, A Newly Approved non-βlactam βlactamase Inhibitor Drug, In Combination Use With Ceftazidime. Drug Res (Stuttg). 2019;69(5):245-255. doi:10.1055/a-0748-5548

24 Mermer S, Aydemir S, Ozgiray E, Sipahi OR. Carbapenem-resistant Klebsiella pneumoniae meningitis: A case report. *J Chemother*. 2016;28(5):454-455. doi:10.1179/1973947815Y.0000000020

25 Chen Y, Liu L. The treatment of nosocomial meningitis and brain abscess by carbapenem-resistant *Klebsiella pneumonia*. Br J Neurosurg. 2019;1-3. doi:10.1080/02688697.2018.1530729

26 Patrial YC, Tortorelli LP, Rodrigues ACS, et al. Post-neurosurgical meningitis caused by KPC-producing Klebsiella pneumoniae: report of two cases. Rev Inst Med Trop Sao Paulo. 2019;61:e69. doi:10.1590/S1678-9946201961069

27 Gofman N, To K, Whitman M, Garcia-Morales E. Successful treatment of ventriculitis caused by *Pseudomonas aeruginosa* and carbapenem-resistant *Klebsiella pneumoniae* with i.v. ceftazidime-avibactam and intrathecal amikacin. Am J Health Syst Pharm. 2018;75(13):953-957. doi:10.2146/ajhp170632

28 Holyk A, Belden V, Lee JJ, et al. Ceftazidime/avibactam use for carbapenem-resistant Klebsiella pneumoniae meningitis: a case report. J Antimicrob Chemother. 2018;73(1):254-256. doi:10.1093/jac/dkx358

29 Daccò V, Claut L, Piconi S, et al. Successful ceftazidime-avibactam treatment of post-surgery Burkholderia multivorans genomovar II bacteremia and brain abscesses in a young lung transplanted woman with cystic fibrosis. Transpl Infect Dis. 2019;21(3):e13082. doi:10.1111/tid.13082

30 Shields RK, Potoski BA, Haidar G, et al. Clinical Outcomes, Drug Toxicity, and Emergence of Ceftazidime-Avibactam Resistance Among Patients Treated for Carbapenem-Resistant Enterobacteriaceae Infections. Clin Infect Dis. 2016;63(12):1615-1618. doi:10.1093/cid/ciw636

31 Samuel S, Edwards NJ, Rojas LJ,et al. "Abstract: Ceftazidime-avibactam for the treatment of post-neurosurgical meningitis caused by a KPC-producing Klebsiella pneumoniae (IDWeek 2016)," Open Forum Infect Dis 2016*; 3(Suppl 1):1182.* [Online]. Available: https://idsa.confex.com/idsa/2016/webprogram/Paper58791.html. [Accessed: 20-Aug-2021].

32 Yasmin M, Hanrahan J, Marshall S, et al. Using Therapeutic Drug Monitoring to Treat KPC-Producing *Klebsiella pneumoniae* Central Nervous System Infection With Ceftazidime/Avibactam. Open Forum Infect Dis. 2020;7(9):ofaa349. doi:10.1093/ofid/ofaa349

33 Pektezel MY, Isikay I, Gocmen R, Inkaya AC. Carbapenem-resistant Klebsiella pneumoniae meningitis and abscess treated with ceftazidime-avibactam . Enferm Infecc Microbiol Clin (Engl Ed). 2021;S0213-005X(21)00083-5. doi:10.1016/j.eimc.2021.03.014