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Maullon, VES, Velasco-Aro SJ. *Outcomes of the use of Ceftazidime-avibactam among patients admitted in the neonatal intensive care unit with multidrug-resistant Klebsiella hospital-acquired sepsis*
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ORIGINAL ARTICLE

OUTCOMES OF THE USE OF CEFTAZIDIME-AVIBACTAM AMONG PATIENTS ADMITTED IN THE NEONATAL INTENSIVE CARE UNIT WITH MULTI-DRUG RESISTENT KLEBSIELLA HOSPITAL-ACQUIRED SEPSIS

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ABSTRACT

Background: The use of ceftazidime-avibactam (CAZ-AVI) has been recently introduced to combat multidrug-resistant organisms (MDROs) in the pediatric population. Case reports have documented the successful off-label use of CAZ-AVI in the treatment of MDRO sepsis in neonates; however, data remains to be limited, especially in the Philippines.

Objectives: This study aims to explore the effects of CAZ-AVI on clinical outcomes including mortality rate, length of hospital stay since treatment initiation, and bacteriological eradication among patients admitted at the NICU with MDR Klebsiella hospital-acquired sepsis. Other objectives include comparing these outcomes between those who received CAZ-AVI (in combination with aztreonam, ATM) and those who received other 2nd line MDR-antibiotic regimens used for carbapenem-resistant Klebsiella growths, as well as exploring the association of factors such as gestational age and age at sepsis diagnosis of patients with their outcomes post-treatment with CAZ-AVI ± ATM.

Methodology: This is a retrospective cohort study of admitted patients in a neonatal intensive care unit of a tertiary hospital with MDR Klebsiella hospital-acquired sepsis across a two-year period. A review of medical records was done, and data were collected and analyzed.

Results: There were a total 11 patients treated with CAZ-AVI ± ATM compared with 11 patients given other 2nd line antibiotic treatment regimens. The use of CAZ-AVI ± ATM exhibited a trend towards a decreased mortality rate (54.5%, $p = 0.17$), shorter length of hospital stays from treatment initiation (30.7 days, $p = 0.50$), and increased bacteriological eradication rates (63.6%, $p < 0.05$), compared with other 2nd line antibiotic treatment regimens, regardless of gestational age and age at sepsis diagnosis.

Conclusion: The use of CAZ-AVI ± ATM showed a more favorable trend compared with other 2nd line antimicrobials for with MDR Klebsiella hospital-acquired sepsis. These observations, however, require further confirmation with a prospective study, a longer study period, and an increase in sample size.

KEYWORDS: *Ceftazidime-avibactam, multidrug-resistant Klebsiella hospital-acquired sepsis, neonates*

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The authors declare that the data presented are original material and have not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and that the authors have met the requirements for authorship.

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INTRODUCTION

Multidrug resistant organisms (MDROs), especially extended-spectrum β-lactamase (ESBL)-producing gram-negative bacilli (GNB) and carbapenem-resistant Enterobacteriaceae (CRE), are among the pathogens implicated in the development of hospital-acquired sepsis in neonatal intensive care units (NICUs). They pose a continuous threat in the management of neonates, especially those with prolonged stays. The problem of antimicrobial resistance among these isolates complicates the management of these infections; as such, the use of novel antibiotics such as ceftazidime-avibactam (CAZ-AVI) have been introduced to help counter these multidrug-resistant organisms. CAZ-AVI, a combination of a third-generation cephalosporin, ceftazidime with a novel beta-lactamase inhibitor avibactam, has been approved in March 2019 by the US Food and Drug Administration (FDA) for use in pediatric patients aged 3 months to 2 years for the treatment of complicated intraabdominal infections in addition to metronidazole, and for complicated urinary tract infections, including pyelonephritis.[1] Its efficacy is attributed to its two-pronged action, with ceftazidime blocking peptidoglycan synthesis through binding with penicillin-binding proteins of gram-negative bacteria, resulting in instability of the cell wall leading to cell death, and avibactam decreasing the availability of active enzymes for hydrolysis by covalently binding to the β-lactamase hydroxyl group, leading to decreased inactivation of the β-lactam antibiotic. Avibactam has shown excellent in vitro activity against multiple β-lactamases, including ESBL and *Klebsiella pneumoniae* carbapenemase (KPC), which is implicated in the increasing virulence of CREs.[2]

Case reports have shown that the use of CAZ-AVI in neonates, albeit off-label, have been safe and effective in treating MDROs. Nascimento et al.[3] described a 29-weeker neonate diagnosed with an MDR *Klebsiella pneumoniae* bloodstream infection (BSI) on his 46th hospital day given CAZ-AVI, with noted culture-proven bacteriological eradication after 14 days of treatment. Asfour et al.[4] detailed how CAZ-AVI was used in the treatment of CRE bacteremia in two extremely premature neonates achieving clinical cure and culture-proven bacteriological eradication. Coskun & Atici [5] also reported how a 27-weeker neonate with PDR *Klebsiella pneumoniae* urinary tract infection that was successfully treated with CAZ-AVI for 10 days, with complete bacteriological eradication and no reported recurrence. A single center retrospective case series by Iosifidis et al.[6] details how eight pediatric patients, including six neonates with XDR/PDR *K. pneumoniae* BSIs underwent treatment with CAZ-AVI and achieved clinical and microbiologic response in all patients. There were no adverse effects attributed to the use of CAZ-AVI in the above reports.

However, the addition of CAZ-AVI to the clinician's armamentarium of antimicrobials against MDROs is already met with increasing trends of resistance to CAZ-AVI, both in vitro and clinically, and have been reported in various centers worldwide.[7] Locally, strains of *K. pneumoniae* producing metallo-β-lactamases (MBLs) such as the New Delhi metallo-β-lactamases (NDM) and class D serine β-lactamases such as oxacillinase (OXA), both of which inactivate carbapenems more avidly, have been documented.[8,9,10] In a study done in five Philippine neonatal ICUs, *K. pneumoniae*, among other gram-negative bacteria like Pseudomonas and Burkholderia, were identified in 94% of samples of culture-proven neonatal sepsis cases, with varying degrees of resistance to cephalosporins and piperacillin-tazobactam.[11] In a 2021 report by Carlos, et al., *K. pneumoniae* carrying the $bla_{\text{CTX-M-15}}$ (76.8%) and $bla_{\text{NDM-1}}$ (37.5%) strains were found to be responsible for outbreaks of MDR *K. pneumoniae* in various Philippine neonatal ICUs from 2015 to 2017.[12] Considering these reports, the introduction of CAZ-AVI in hospital formularies in the Philippines is a welcome development in the battle against AMR, as CAZ-AVI has been shown to be effective in neutralizing extended-spectrum β-lactamases and MBLs (such as CTX-M and NDM, respectively). Furthermore, like how aminoglycosides are used in conjunction with cephalosporins or carbapenems in the treatment of gram-negative infections, the practice of adding aztreonam (ATM) to the use of CAZ-AVI has been instituted in centers utilizing the latter to combat CREs. The combination is posited to work as avibactam inhibits the carbapenemases (Ambler class A and D enzymes) that frequently hydrolyze ATM despite its inherent resistance to degradation by MBLs.

Studies on the use of CAZ-AVI with or without ATM in the neonatal population have been limited to case reports and observational studies, with no local data available. Considering the growing number of MDR Klebsiella infections in the NICU of a tertiary government

hospital, this is the first local study to explore the effects of CAZ-AVI on clinical outcomes- namely mortality rate, length of hospital stay since treatment initiation, and bacteriological eradication of patients admitted at the NICU with MDR Klebsiella hospital-acquired sepsis. This study will also compare these outcomes between those who received CAZ-AVI ± ATM and those who received other 2nd line MDR-antibiotic regimens, as well as explore the association of factors such as gestational age and age at sepsis diagnosis of patients with their outcomes post-treatment with CAZ-AVI ± ATM.

METHODOLOGY

Study Design

This is a retrospective cohort study of patients admitted at the Neonatal Intensive Care Unit of a tertiary government hospital from January 2022 to December 2023 with culture-proven MDR *Klebsiella* hospital-acquired sepsis.

Participants

Participants include a cohort of patients, admitted at the Neonatal Intensive Care Unit of a tertiary government hospital as per data collected from the census of its Section of Infectious and Tropical Diseases, supported with electronic medical records obtained from the Medical Records Division. A sample size calculation was not performed due to the limited number of eligible participants during the study period owing to CAZ-AVI's limited use as of writing; therefore, all individuals who met the inclusion criteria and with data available within the specified timeframe were included in the study.

Inclusion Criteria: Patients aged 0-120 days (to accommodate extremely preterm neonates acquiring HAIs late in their course necessitating the use of CAZ-AVI), admitted from January 2022 to December 2023 with culture-proven MDR Klebsiella hospital-acquired sepsis treated with CAZ-AVI (n = 11, among which: with aztreonam n = 9, and without aztreonam n = 2) OR other 2nd line antibiotic regimens (n = 11, with a combination of any of the following: ciprofloxacin, levofloxacin, metronidazole, polymyxin B, amikacin, aztreonam, ampicillin-sulbactam, gentamicin, or any combination of these) were included in the study. Those with extremely- (not susceptible to all but one or two classes of antimicrobials) and pan-drug (not susceptible to all classes of antimicrobials) resistant microbial growths were also included in the study.

Exclusion Criteria: Patients not meeting the age cut-off, as well as those diagnosed with drug-susceptible and clinical MDRO hospital-acquired sepsis were excluded from the study. Patients qualifying for the use of CAZ-AVI but died prior to administration, as well as those who experienced adverse effects from the administration of CAZ-AVI were also not included. Those with Klebsiella pneumoniae pneumonia, clinical MDRO sepsis, and MDR sepsis caused by other Enterobacteriaceae species (e.g., Serratia marcescens, Escherichia coli, and Enterobacter cloacae) treated with ceftazidime-avibactam were also not included in the study.

Withdrawal Criteria: N/A

Operational Definition of Terms

1. Baseline characteristics – this will include the sex and associated comorbidities of the patients included in the study.
2. Risk factors
   a. *Gestational age* – duration of pregnancy before birth based on the mother's last normal menstrual period or the fetus' biometric parameters taken during ultrasound examination. Births are then classified as per the classification of deliveries set by the American College of Obstetricians and Gynecologists: extremely preterm (<28 weeks), very preterm (28 to 31 weeks and 6 days), moderately preterm (32 to 33 weeks and 6 days), late preterm (34 to 36 weeks and 6 days), and early term (37 to 38 weeks and 6 days).
   b. *Age at sepsis diagnosis* – the patient's age in days where the first clinical signs or microbiological evidence of Klebsiella bacteremia first appeared
3. MDR hospital-acquired sepsis – culture-proven bacteremia that lacks susceptibility to at least one agent in three or more antimicrobial classes acquired during a hospital admission, at least 48 hours from admission
4. Mortality rate – the total number of deaths attributable to MDR *Klebsiella* hospital-acquired sepsis divided by the total number of patients included in the study

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5. Length of hospital stay – number of days spent by a patient admitted at the hospital since diagnosis of MDR *Klebsiella* hospital-acquired sepsis until their discharge or mortality
6. Bacteriological eradication – negative bacterial blood cultures on Day 7 of antibiotic treatment with either CAZ-AVI ± ATM or other 2nd line antibiotic regimens

Statistical Analysis

Data was inputted on a Google Sheets file only accessible to the primary investigator, where statistical analysis, both descriptive (via computation of means) and inferential (via both paired and independent t-tests, depending on the sample size of the variables being measured) were done. All variables were checked for completeness and accuracy prior to analysis, and any missing data were not replaced nor filled in. P-values less than 0.05 were considered statistically significant. Confidence intervals and odds ratios were not used due to the small sample size between groups.

Bias and Limitations of the Study

The data included in this study were affected by the degree of accuracy and completeness in the reporting and documentation in the census of the Section of Infectious and Tropical Diseases of the hospital's Department of Pediatrics, as well as in the electronic medical record entries made by the attending physicians. The study is also limited by a small sample size due to few culture-proven cases of Klebsiella HAIs, as well as due to the limited availability and use of CAZ-AVI in the research setting.

Ethical Considerations

Names encountered during data collection have been anonymized prior to encoding, processing, and analysis using a password-protected Microsoft Excel file saved in a computer owned by the primary investigator. The investigators presented the study protocol to the Institutional Ethics Review Board, which subsequently approved the protocol. As this study only employs census and chart reviews, and any personal identifiers anonymized, an informed consent was not necessary. The research presents no more than minimal risk (e.g., breach of de-identified data) and will not affect the rights and welfare of the participants. The investigators declare no conflicts of interest, potential or actual, in any form in the conduct of this study, as well as any funding or grants provided by third parties.

RESULTS

Table 1 shows the baseline characteristics of the patients included in the study.

Table 1. Baseline characteristics of patients admitted at the NICU diagnosed with culture-proven MDR Klebsiella sepsis.

Baseline Characteristics	CAZ-AVI ± ATM (n = 11)	Other 2nd Line Antibiotic Regimens (n = 11)	*p* values
Sex			0.34
Male	8	6	
Female	3	5	
Comorbidities			
Respiratory	6	7	
Gastrointestinal	3	1	
Neurologic	3	4	
Hematologic	2	0	
Renal	1	2	
Cardiac	1	1	
Genetic	1	1	
Endocrine	0	1	

Analysis of the patients' medical records showed that clinical outcomes, depending on risk factors-namely: gestational age and age at sepsis diagnosis were not statistically significant between those who received CAZ-AVI ± ATM versus those who received other 2nd line antibiotic regimens. Mortality rate, length of hospital stay since sepsis diagnosis, and bacteriological eradication since treatment initiation were consistent between treatment groups among extremely and very preterm infants, as well as among moderately preterm, late preterm, and early term infants. The same observation was also found when groups were compared depending on their age when they were diagnosed with MDR Klebsiella sepsis, as seen in Table 2.

There is a trend towards decreased mortality rates seen regardless of gestational age in the CAZ-AVI ± ATM group, versus the group given other 2nd line antibiotic regimens. The length of hospital stay after sepsis diagnosis for extremely and very preterm neonates were noted to have shorter lengths of hospital stay compared to their older counterparts mainly due to their increased mortality rates (i.e., hospital stays were shorter as patients die before antibiotic completion). Bacteriological eradication rates were similar regardless of gestational age with the CAZ-AVI ± ATM group, exhibiting 100% bacteriological eradication versus a mean of 62.5% for those given 2nd line antibiotic regimens.

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Table 2. Risk factors of patients admitted at the NICU diagnosed with culture-proven MDR Klebsiella sepsis and response to antimicrobial therapy.

Risk Factors	CAZ-AVI ± ATM (n = 11)	Other 2nd Line Antibiotic Regimens (n = 11)	*p*-values
Gestational Age			
Mortality (in %)			
Extremely & Very Preterm (n = 9)	75%	100%	0.20
Moderately & Late Preterm, Early Term (n = 13)	33%	57%	0.22
LOS (in days)			
Extremely & Very Preterm (n = 9)	13.4	9.75	0.31
Moderately & Late Preterm, Early Term (n = 13)	45.17	42.86	0.47
Bacteriological Eradication (in %)			
Extremely & Very Preterm (n = 9)	100%	66.7%	0.19
Moderately & Late Preterm, Early Term (n = 13)	100%	60%	0.10
Age at Sepsis Diagnosis			
Mortality (in %)			
<2 weeks (n = 7)	25%	33.3%	0.42
2-4 weeks (n = 7)	50%	100%	0.10
>4 weeks (n = 8)	100%	80%	0.24
LOS (in days)			
<2 weeks (n = 7)	30.25	51	0.22
2-4 weeks (n = 7)	48	12.67	0.17
>4 weeks (n = 8)	8.33	29.6	0.27
Bacteriological Eradication (in %)			
<2 weeks (n = 7)	100%	66.7%	0.19
2-4 weeks (n = 7)	100%	50%	0.21
>4 weeks (n = 8)	100%	66.7%	0.25

Overall, the use of CAZ-AVI ± ATM exhibited a trend towards a decreased mortality rate (54.5%, p = 0.17), shorter length of hospital stay since treatment initiation (30.7 days, p = 0.5), and increased bacteriological eradication (63.6%, $p < 0.05$) compared with other 2nd line antibiotic treatment regimens. Only the difference in bacteriological eradication was statistically significant between groups as seen in Table 3.

Table 3. Clinical outcomes of patients admitted at the NICU diagnosed with culture-proven MDR Klebsiella sepsis treated with CAZ-AVI and other 2nd line antibiotic regimens.

Clinical Outcomes	CAZ-AVI ± ATM (n = 11)	Other 2nd Line Antibiotic Regimens (n = 11)	*p*-values
Mortality (in %)	54.5%	72.7%	0.17
LOS (in days)	30.72	30.82	0.50
Bacteriological Eradication (in %)	63.6%	45.4%	**0.04**

DISCUSSION

Despite being approved for use in patients aged 3 months and above, the off-label use of CAZ-AVI (with or without aztreonam) in neonates with MDR Klebsiella infections has been shown to produce clinical cure and culture-proven bacteriological eradication in various case reports and series over the last few years. [3,4,6] However, in the neonatal population, numerous factors need to be considered to contextualize the efficacy of the use of CAZ-AVI. Factors such as gestational age and age at sepsis diagnosis can influence clinical outcomes most especially when mortality or survival rates are being measured.

It has been established in existing literature that gestational age is inversely proportional to mortality rates in neonatal sepsis, that being extremely and very preterm neonates exhibit higher mortality rates compared to older neonates[13], and that preterm births are a significant risk factor in the development of neonatal sepsis.[14,15] This trend is likewise seen in our sample population, where extremely and very preterm neonates showed a higher mortality rate across both antibiotic treatment groups, compared to older preterm and early term neonates.

Extremely and very preterm neonates were also more likely to not complete antibiotic regimens due to mortality while ongoing treatment, leading to shorter lengths of hospital stay, compared with older preterm and early term neonates who were able to respond and recover from their infections. Gestational age also did not seem to be associated with changes affecting bacteriological eradication in the sample population as the use of CAZ-AVI ± ATM showed trends of higher eradication rates compared with other 2nd line antibiotic regimens, regardless of gestational age.

Another identified risk factor for the development of neonatal sepsis and subsequent morbidity and mortality is age at sepsis diagnosis. Neonatal sepsis has been shown to be associated with mortality when acquired during the first few days of life.[16] Additionally, a review of 125 articles on hospital-acquired infections from low- and high-resource setting neonatal intensive care units showed that neonatal age and gestational age are both risk factors for the development of hospital-acquired infections.[17] Contrary to these, an increase in mortality rates in our sample was seen among those who have contracted hospital-acquired infections at >4 weeks of age, well beyond the period defined as early-onset.

A plausible explanation for this increase in mortality rate among older neonates (as seen in our population) is that complications from existing comorbidities and documented antimicrobial resistance (sometimes elicited from a history of non-response to previous antibiotic regimens) may preclude adequate response to antibiotics among older neonates. As a result, the sepsis that develops may prove to be overwhelming, causing significant morbidity and mortality. This is corroborated by a retrospective cohort study by Afonso, et al.[18], which identified late-onset sepsis as a risk factor for mortality in late preterm neonates, probably because preterm neonates who survive their first few weeks of life are more likely to be exposed to sepsis and other associated adverse events later in their hospital course. [19] Additionally, the initial use of inappropriate or ineffective empiric antibiotic regimens upon sepsis diagnosis also poses a risk in the increased mortality rate among those diagnosed with late-onset neonatal sepsis, as documented by Miselli, et. al. [20]

Akin to comparison between gestational ages, a trend of decreased lengths of hospital stay is seen among groups with increased mortality rates regardless of age at sepsis diagnosis, with some patients in the sample population succumbing to sepsis before completing their antibiotic regimens. Similarly, bacteriological eradication rates among the CAZ-AVI group also remain consistently high between antibiotic treatment groups, highlighting CAZ-AVI's potential as an effective antimicrobial agent for MDR hospital-acquired sepsis for neonates regardless of the onset of infection.

When compared with the other 2nd line antibiotic treatment regimens, the use of CAZ-AVI in the overall neonatal cohort included in this study generally exhibited trends towards decreased mortality rates, shorter lengths of hospital stay since treatment initiation, and increased bacteriological eradication rates. This bolsters evidence supporting the use of CAZ-AVI in the neonatal population, building on previous case reports[3,4,5] and single- and multiple-center observational studies in both adults[21,22,23] and neonates[24] on the efficacy and safety profile of CAZ-AVI against MDR, and even pan-drug resistant[6,25] organism infections.

The concomitant use of the monobactam aztreonam (ATM) with CAZ-AVI in our sample population could have also contributed to the positive clinical outcomes associated with the use of CAZ-AVI. Previously reported by Davido et al.[26] as a salvage therapy for MBL-producing CREs, the use of CAZ-AVI with ATM has also been suggested as an option in the treatment of CRE infections in children. [27,28] Considering the available supporting evidence on the effectivity of CAZ-AVI ± ATM in the local neonatal population as can be gleaned from the findings in this study, it is thus reasonable to suggest that this antibiotic regimen be included in local frameworks for antibiotic selection as an option against hospital-acquired Enterobacteriaceae infections, with or without carbapenem resistance.

This study has several limitations, primarily, a small sample size due to the limited use of CAZ-AVI in the research setting as of writing. The participants in the cohort where CAZ-AVI was used with or without aztreonam were also grouped together during data analysis, notwithstanding the effects of aztreonam having a possible considerable value to affect that cohort's outcome. Due to the growing problem of increasing antimicrobial resistance and CAZ-AVI being a potential alternative treatment for MDRO infections, CAZ-AVI is recommended to be made more available, especially in critical care settings. More clinical evidence is needed but the positive trend in our study shows the CAZ-AVI ± ATM combination to be an equally, or potentially more effective treatment for MDR Klebsiella hospital-acquired infections.

CONCLUSION

Results from an analysis of our limited data show that the use of CAZ-AVI ± ATM among neonates with culture-proven MDR Klebsiella hospital-acquired sepsis exhibited a trend towards a decreased mortality rate, shorter length of hospital stay since treatment initiation, and increased bacteriological eradication rates compared with other 2nd line antibiotic treatment regimens, regardless of gestational age and age at sepsis diagnosis. It is therefore recommended to include the CAZ-AVI ± ATM combination as an option against CRE infections in neonates in frameworks on the selection of antibiotic therapy, especially in institutions with documented increasing antimicrobial resistance rates. Direction of future studies may be geared towards a review of clinical outcomes among a more expanded population, as well as surveillance reports on nascent local resistance patterns against CAZ-AVI.

CONFLICT OF INTEREST

None declared.

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