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An Insight into the Use of Novel Antibiotic Regimes for Post Neurosurgical Meningitis a Case Report and Review of Literature

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Abstract

Central nervous system (CNS) infections are associated with high mortality rates, morbidity, limited antibiotic treatment options, and high cost of therapy especially in low and middle-income countries. Post-neurosurgical infections are often associated with multi-drug resistant organisms. Given the limited options of antibiotics due to blood-brain and blood-cerebrospinal fluid (CSF) barriers, exploring various antibiotic combinations including the latest ones is imperative. Drugs like Ceftazidime- Avibactam and Aztreonam may be useful in carbapenem-resistant gram-negative infections. More robust studies may be designed to offer better treatment options for difficult CNS infections.

Keywords: Ceftazidime Avibactam; Antibiotic Regimes; Infections; Hospitalization

Abbreviations

CNS: Central Nervous System, CSF: Cerebrospinal Fluid, PCNSI: Postoperative Central Nervous System Infections; XDR: Extended Drug Resistant; CRE: Carbapenemase-Producing *Klebsiella pneumoniae*.

Introduction

Bacterial meningitis and other central nervous system (CNS) infections are associated with high mortality rates, morbidity, limited antibiotic treatment options, and high cost of therapy especially in low and middle-income countries [1]. Post-operative central nervous system infections (PCNSI) are dreaded complications in neurosurgical patients and pose a challenge in the neurocritical care unit. Incidence varies from 0.5-8% in craniotomy and shunt procedures [2,3]. In contrast, the post-spinal surgery infection rates may be as high as 18% depending upon the site, type of surgery, and the presence of implants [4]. PCNSI are difficult to diagnose. Response to antibiotic therapy is unpredictable due to blood-brain and blood-cerebrospinal fluid (CSF) barriers and the growing antibiotic resistance. There is no consensus regarding the choice and duration of antibiotics. The presence of the blood-brain barrier and drug toxicity make treatment very challenging, especially for Carbapenem-Resistant Enterobacteriaceae (CRE) meningitis. *Klebsiella pneumoniae* (*K. pneumoniae*) is one of the most common bacteria in healthcare-associated ventriculitis and meningitis [5-7]. The resistance rate of *K. pneumoniae* isolated from CSF to Meropenem is reported to be up to 64.1% in 2018 in China, which is much higher than that from other specimens commonly, lower respiratory, urine, and blood [7,8]. Multidrug-resistant Gram-negative bacilli (MDR-GNB)-related CNS infections are an increasingly prevalent threat with a mortality rate of 70% [8]. Therefore, new antimicrobials are urgently needed to address this clinical problem. Management is often complicated by repeated surgery adding to the morbidity, prolonged hospitalization, financial burden, and poor outcome.

We report a case of post-craniectomy meningitis due to extensively drug-resistant (XDR) Klebsiella successfully treated with a combination of antibiotics. A 42-year-old man was brought to the emergency of our hospital on 6.3.2024 with a history of sudden loss of consciousness, vomiting, and urinary incontinence. On arrival he had a GCS of E1M5V1, left hemiplegia 2/5. Pupils were reacting sluggishly. He was intubated and ventilated. CT scan of the brain revealed a large right frontoparietal intracerebral haemorrhage with midline shift (Figure 1).

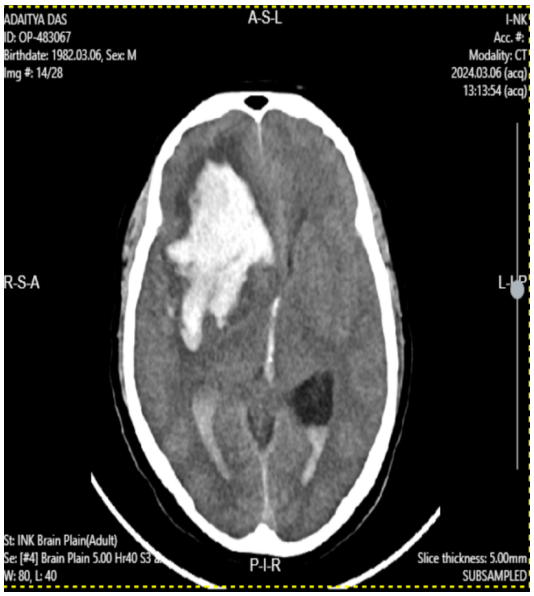

Figure 1: CT Scan Head on Admission Showing Large ICH, IVH.

Left-sided decompressive craniectomy and evacuation of hematoma along with excision of a small arteriovenous malformation was done on 6.3.24. He was started on intravenous (i.v.) Piperacillin – Tazobactum for aspiration pneumonia, subsequently tracheostomy was done. On 9.3.2024 he was spiking fever Antibiotics were escalated to i.v. Meropenem. For two weeks he continued to have intermittent fever despite various antibiotic regimes. Tracheostomy secretion, urine, and blood cultures returned negative. In the next few days, he became hypotensive. The surgical site started oozing pus on 4.4.2024. Lumbar puncture CSF revealed frank meningitis (Table 1), there was a large collection at the surgical site (Figure 2).

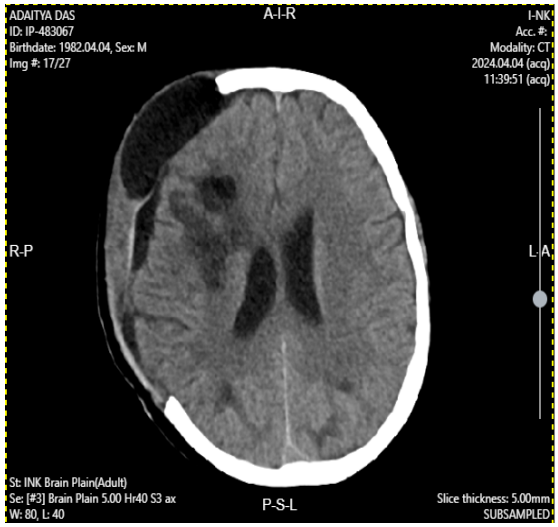

Figure 2: CT Scan Head on Showing Large Subgaleal and Intracerebral Collection.

Pus culture grew XDR (extended drug resistant) Carbapenemase-producing *Klebsiella pneumoniae* (CRE). As these organisms are resistant to all antibiotics and Polymyxins are of large molecular weight with poor CSF penetration, a combination regime of Ceftazidime-Avibactam (2.5gm) i.v. thrice with Aztreonam (2gm) i.v. infusion, each simultaneously over two hours each was started. Meropenem (2 gm) i.v. thrice daily was added. This combination has been reported to be successful in CRE including metalobetalactamases and has been used for pneumonias as well as urinary tract infections. The patient clinically improved and became afebrile. Serial CSF showed steady improvement (Table 1).

CSF	4.4.2024	9.4.2024	14.4.24	24.4.2024
Cell count(/cmm)	11575 (P-95%, L-5%)	2250 (P-90%, L-10%)	754(P-90%, L-10%)	18 (All L)
P-polymorphs				
L-lymphocyte				
Glucose(mg/dl)	01 (blood glucose- 130)	28 (blood glucose-123)	41(blood glusose-126)	62(blood glucose -160)
Protein(mg/dl)	1215	222	317	92
Lactate (mmol/L)	21.71	9.1	5.27	3.44

Table 1: Serial CSF Picture.

Wound debridement was done twice and finally, secondary suturing was done on 24.4.2024. The patient was discharged home to complete antibiotics for a total of six weeks,

Discussion

Ceftazidime-Avibactam (CAZ-AVI), a combination of the anti-pseudomonal cephalosporin Ceftazidime and the novel b-lactamase inhibitor Avibactam, has in vitro activity against a broad range of Gram-negative bacteria especially Enterobacteriaceae. AVI protects CAZ against degradation by *Klebsiella pneumoniae* carbapenemases, AmpC cephalosporinases, OXA-48, and ESBLs (eg, TEM, SHV, and CTX-M) to expand the antibacterial activity spectrum but not against metallo-b-lactamase (MBL) producers. It has been approved for use in complicated intraabdominal infections, urinary tract infections, and pneumonia including hospital and ventilator-associated pneumonia due to MDR organisms. The penetration of Ceftazidime across the blood-brain barrier is poor, but this increases if the meninges are inflamed. Mean CSF CZA-AVI penetration is 38% [5-7]. In some European countries, CAZ-AVI has been approved for infections with limited treatment options which include bacterial meningitis. Both Ceftazidime and Avibactam have been reported to have a high mean CSF penetration and the combination effectively suppresses CSF bacterial loads. Yasmin, et al. reported TDM of CAZ-AVI, showing that at 64 min after a 2-h infusion, CAZ and AVI concentrations were 19.0 and 4.2 μg/mL in the CSF and 61.3 and 13.1 μg/mL in the plasma, respectively [7,8]. The guidelines for hospital-acquired CNS infections recommend a CSF level 10 times higher than the in vitro MIC (minimum inhibitory concentration). There are numerous reports of the use of CAZ–AVI for post-operative meningitis [4-7].

Our experience was unique as probably this triple combination has hardly been used for resistant post-neurosurgical Klebsiella meningitis. There were limitations. CAZ-AVI in meningitis is an off-label use, we combined it with Aztreonam and Meropenem to combat all resistant enzymes. CAZ- AVI and Meropenem combination are synergistic [9]. Moreover, as cephalosporins as a group are neurotoxic causing encephalopathy as well as aseptic meningitis, the level or dose of the drug causing toxicity is still unknown [10]. In India drug levels in CSF are hardly available. Hence therapeutic levels could not be determined.

Conclusion

Post neurosurgical site infections are difficult to diagnose and treat. The use of CAZ-AVI for hospital-acquired meningitis needs to be explored. Combination with Aztreonam and high-dose Carbapenem may be a solution for highly drug-resistant organisms. The importance of surgical intervention for source control in sepsis needs emphasis as in our patient.

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