ORIGINAL ARTICLE

Clinical and microbiological characteristics and outcome of patients with healthcare associated ventriculitis and meningitis at a Public Sector Hospital in Pakistan

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ABSTRACT

Background: Healthcare-associated meningitis and ventriculitis (HAVM) is a serious complication of placement of ventriculoperitoneal shunt (VPS) and external ventricular device (EVD), and can incur high morbidity and mortality.

Material And Methods: This retrospective descriptive, single center study was conducted in patients who had placement of VPS or EVD between January 2018 and December 2021 and developed HAVM. A list of these patients was retrieved from records maintained by the neurosurgery department.

Results: Thirty patients with HAVM were included. Median age was 8.5(IQR 22.25-0.75), two thirds were pediatric, 50% were males. Indication for device placement was congenital hydrocephalus in 18 (60%), tumor in 6 (20%) with VPS insertion in 25 (83.3%), EVD in 5 (16.7%). Fever was documented in 29 (96.7%). Cerebrospinal fluid analysis (CSF) demonstrated median pleocytosis with IQR of 93.5 (17-12959), protein of 131 (IQR 2-285), glucose of 24.5 (IQR 0-72). 17 (56.6%) had ICU stay, 11 were on mechanical ventilation. Mortality occurred in 4 (13.3%). CSF cultures were positive in 28 (93%) patients. Of 32 bacterial isolates, 16 were gram positive and 16 gram negative. In 15 (93.7%) patients, gram negatives were resistant to carbapenems and included 7 (46.6%) Enterobacterales (CRE), 3 (20%) *Pseudomonas aeruginosa* and 5 (33.3%) *Acinetobacter spp*. They were treated with IV colistin and meropenem. Predictors of mortality were male sex and sepsis. ($p \leq 0.05$).

Conclusion: Male sex and sepsis were found to be predictors of mortality in HAVM. Gram negatives in CSF cultures of 15 (93.7%) patients were resistant to carbapenems and challenging to treat.

Keywords: Cerebrospinal fluid infection, Healthcare-associated meningitis and ventriculitis, Hydrocephalus management, Risk-factors, Shunt infections

BACKGROUND

Healthcare-associated meningitis and ventriculitis (HAVM) is a known complication of invasive neurosurgical procedures and is associated with high morbidity and mortality.[1] One of the most commonly employed neurosurgical intervention is placement of ventriculoperitoneal shunt (VPS) or external ventricular drainage (EVD) catheter in acute hydrocephalus.[2] Depending on the location and the kind of neurological device employed, ventriculitis epidemiology varies, with some studies showing a 20% prevalence rate.[3] VPS related cerebrospinal infection rates ranging from 2.2% to 41% have been reported.[4] Reported rates of EVD-related infections range from 3%-19%.[5] HAVM prolongs duration of hospitalization and overall cost, increases morbidity and mortality and worsens prognosis.[6-8] Moreover, in a critical care setting, HAVM is increasingly caused by multi-drug resistant organisms (MDRO) which are challenging to treat.[9] There is limited data from Pakistan regarding HAVM. This study was conducted in order to identify the clinical presentation, microbial etiology, management and factors associated with poor outcome in patients who develop HAVM with the goal to contribute to guidelines for the most appropriate empirical antimicrobial therapy, and to improve management and outcomes.

MATERIAL AND METHODS

This is a retrospective descriptive study in patients diagnosed with HAVM. The Benazir Bhutto Institute of Trauma is a 500-bed facility that is located in the

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southern port city of Karachi in Sindh, Pakistan and is a major referral center for the provinces of Sindh and neighboring Baluchistan. It is a public sector government funded hospital, and one of few trauma centers in the country.

A list of all patients who had placement of either VPS or EVD between January 2018 and December 2021 was retrieved from records maintained by the neurosurgery department. Those patients that developed HAVM were further identified. from the list and their medical records reviewed to determine if they met our study criteria.

Our inclusion criteria incorporated patients that were admitted to the Institute of Trauma and had placement of the VPS or EVD at the facility, and subsequently developed HAVM. All ages, including infants, pediatric (1-17 years) and adults were included. Patients with HAVM were excluded if they had placement of VPS or EVD at an outside facility but had been transferred to our institute. In addition, patients with community-acquired meningitis, subdural empyema, brain abscess, or tuberculous meningitis were excluded even if they had placement of the ventricular catheter at our facility as part of their management. Those with missing pertinent data were also excluded.

We diagnosed healthcare-associated meningitis and ventriculitis if CSF culture was positive, or if there were at least 2 signs and symptoms such as fever >38.0 °C, headache or meningeal signs along with abnormal CSF analysis with pleocytosis, elevated protein, and decreased glucose. Diagnosis of HAVM by an Infectious Diseases specialist was also included in the definition, if above conditions were met.

Recovery from HAVM was documented when there was resolution of symptoms and signs of CNS infection and CSF cultures remained negative at completion of antimicrobial therapy with no relapse of infection during the admission.

The admission diagnosis, demographics, co-morbidities, type of ventricular catheter whether VP or EVD, indication for use, whether inserted in the emergency or elective setting, were recorded. Health care-associated infections such as pneumonia, central line bloodstream infection, and catheter-associated urinary tract infection were also entered into the data base. The number of intracranial surgeries, removal or revision of the device, empirical antimicrobial therapy, and duration of ICU and hospital stay were noted. Laboratory data including CSF parameters of cell count, biochemistry, and microbiology were abstracted from the patients' electronic medical records.

The primary outcome of this study was in-hospital mortality, whereas secondary outcomes included ICU admission, mechanical ventilation, sepsis, length of ICU stay, duration of hospitalization and readmission for the same diagnosis. Ethical approval was obtained from the institutional ERC prior to conducting the study. All data entered in the computer were password secured (Author/PI had access only). No personal identifiers of patients were recorded.

Data were stored and analyzed using IBM-Statistical Package for the Social Sciences version 23.0; counts with percentages were given on demographics, co-morbidities, indication for neurosurgical procedure, type of ventricular catheter, placement, pre-operative antibiotics, sign and symptoms at presentation of HAVM and other qualitative parameters of study, Median with Interquartile range was reported for age, length of ICU stay, white cell counts, protein and glucose. Fisher's Exact test was used to check the association of mortality with age, gender, diagnosis, comorbidities, type of device, CSF protein, Type of bacteria in CSF, Cather management, ICU admission, sepsis and mechanical ventilation. p-values less than 0.05 were considered statistically significant.

RESULTS

A total of 30 patients with HAVM were included in the study. The median age and IQR of patients was 7 years (22). Of 30, two-thirds (66.7%) were of the pediatric population, 50% were males.

The most common co-morbidity noted was diabetes mellitus in 6 (20%). None were diagnosed to be immunocompromised. The most common indications for placement of the device were congenital hydrocephalus in 18 (60%) and tumor in 6 (20%).

Initial ventricular catheter placement included a VP shunt in 25 (83.3%) and EVD in 5 (16.7%). Catheter placement procedures were performed in the emergency setting in 8 (26.7%). All patients received peri-operative ceftriaxone. Fever was the most common symptom of HAVM in 29 (96.7%); headache in 14 (46.7%). The most common sign of HAVM was neck stiffness in 6 (20%). Cerebrospinal fluid analysis was significant for a median pleocytosis with IQR of 93.5 cells/mm^3 (17-

12959), protein of 131 mg/dl (2-285) and glucose of 24.5 mg/dl (0-72).

Of 30, 17 (56.6%) had ICU stay and of these 11 were placed on mechanical ventilation. Mortality occurred in 4 (13.3%) patients whereas 26 (86.7%) were considered to have made good recovery and were discharged. None of those discharged were readmitted. Duration of hospital stay was a median of 26 (10-332) (Table-I).

Of 30 patients with HAVM, CSF cultures were positive in 28 (93%) patients. Of 32 bacterial isolates recovered, 16 (50%) were gram positive and 16 (50%) gram negative. The most commonly reported bacteria overall was *Coagulase negative staphylococcus* in 9 (56.25%). Gram negative multi-drug-resistant organisms that were resistant to the carbapenems were isolated in 15 (93.7%) patients and included 7 (46.6%) Enterobacterales (CRE), 3 (20%) "difficult-to-treat" *Pseudomonas aeruginosa* and 5 (33.3%) *Acinetobacter spp*.

All patients were started empirically on intravenous meropenem and vancomycin and therapy was adjusted in accordance with culture and sensitivity results, if indicated. Of 30, 15 (50%) patients received combination of intravenous colistin and meropenem for treatment of gram-negative multi-drug-resistant organisms isolated in CSF culture. None of the patients received intrathecal or intraventricular colistin. Repeat CSF studies were performed, on average, every 72 hours, to document clearance in those with positive CSF cultures, as well as to monitor CSF parameters while on antimicrobial therapy.

Initial catheter management of HAVM included immediate removal of VP shunt or EVD in 4 (13.3%) patients, exteriorization of distal end in 22 (73.3%) of whom 10 (33.3%) subsequently required shunt removal, whereas in 4 (13.3 %) the VP shunt and EVD were left in-situ and treated conservatively with antibiotics alone. Of 30 patients, sepsis was diagnosed in 5 (16.6%). The most common healthcare associated infection documented was pneumonia. Infection at the device insertion site occurred in 2 (6.7%) patients (Table-II).

Four (13.3%) patients died and good recovery was documented in 26 (86.7%) patients. Predictors of mortality were found to be male sex and sepsis. ($p \leq 0.05$). Though not found to be statistically significant, 3 of 4 patients that died had gram negative multidrug resistant organisms recovered in CSF culture. Age, comorbidities, immune status, concomitant infection and mode of procedure, whether elective or emergent, were not found to be statistically significant (Table-III).

Table-I: Demographics, clinical and laboratory characteristics of patients with healthcare associated ventriculitis and meningitis (n=30).

Characteristics	Frequency (%)
Demographics:	
Median Age (IQR):	07 (22)
< 1 year	09 (30%)
1-17 Years	11 (36.7%)
18-65 Years	10 (33.3%)
Gender:	
Male	15 (50%)
Female	15 (50%)
Co-morbidities	
Diabetes Mellitus	06 (20%)
Hypertension	01 (3.3%)
Malignancy	03 (10%)
Indication for Neurosurgical Procedure:	
Tumor	06 (20%)
Post Traumatic hydrocephalus	04 (13.3%)
Intraventricular bleed	01 (3.3%)
Congenital hydrocephalus	18 (60%)
Normal pressure hydrocephalus	01 (3.3%)
Type of Ventricular Catheter:	
VP	25 (83.3%)
EVD	05 (16.7%)
Placement:	
Emergency	08 (26.7%)

Elective	22 (73.3%)
Peri-operative Antibiotics	30 (100%)
Signs and Symptoms at Presentation of HAVM:	
Fever	29 (96.7%)
Altered mental status	09 (30%)
Nausea/Vomiting	03 (10%)
Neck Stiffness	06 (20%)
Headache	14 (46.7%)
Seizures	06 (20%)
Laboratory Parameters	
Positive CSF Culture: (n %)	28 (93%)
Cerebrospinal Fluid: (median ,IQR)	93.5 (17-12959)
Leukocytes (per mm^3)	72
Neutrophils percentage	24.5 (0-72)
Glucose (mg/dl)	131 (2-285)
Protein (mg/dl)	04 (13.3%)
Blood: (n %)	
Positive blood cultures	
Number of neurosurgeries during admission (median, IQR)	2(0-3)
ICU stay	17 (56.6%)
Duration of ICU stay (median, IQR)	7 (1-112)
Mechanical Ventilation	11 (36.7%)
Duration of hospitalization (median, IQR)	26 (10-332)
Outcome	
• Died	04 (13.3%)
• Recovered	26 (86.6%)

Table-II: Microbiological Data and Management of Healthcare Associated Ventriculitis and Meningitis (n=30)

Pathogen	No (%)
Cerebrospinal (CSF) Culture	
No growth	02 (6.7%)
Positive Culture:	28 (93.3%)
• Monomicrobial Growth	24 (85.7%)
• Polymicrobial Growth	04 (14.3%)
Gram Positives:	16 (50%)
Staphylococcus aureus (all MRSA)	05 (31.25%)
Coagulase negative staphylococcus	09 (56.25%)
Corynebacterium spp	02 (12.5%)
Gram Negatives:	16 (50%)
Acinetobacter spp.	05 (31.25%)
Enterobacter spp.	01 (6.25%)
Escherichia Coli	03 (18.75%)
Klebsiella spp	03 (18.75%)
Pseudomonas aeruginosa	03 (18.75%)
Serratia Marcescens	01 (6.25%)
MDRO Gram Negatives	15 (93.7%)
CRE[1]	07 (46.6%)
CRA[2]	05 (33.3%)
DTR-PA[3]	03 (20%)
Blood Culture	
No growth	26 (86.6%)
Coagulase Negative Staphylococcus	02 (6.7%)
Pseudomonas aeruginosa	02 (6.7%)
Concomitant Healthcare Associated Infection:	
None	14 (46.6%)
CLABSI	02 (6.7%)
HAP/VAP	10 (33.3%)
CAUTI	02 (6.7%)

SSSI at VP or EVD Insertion Site	02 (6.7%)
Sepsis	05 (16.6%)
IV Antibiotics given:	
IV Colistin	15 (50%)
Meropenem	18 (60%)
Vancomycin	17 (56.6%)
Catheter Management:	
• Immediate removal of VP shunt or EVD	4 (13.3%)
• Exteriorization of distal end alone.	12 (40%)
• Exteriorization of distal end followed by VP shunt removal.	10 (33.3%)
• VP and EVD not removed with conservative management alone.	4 (13.3%)

Table-III: Predictors of mortality in patients with HAVM (n=30).

Variable	Total Number (n=30)	Mortality n (%) (n=4)	*p* -value
Age			
< 1 year	9 (30%)	0	
1-17 years	11 (36.7%)	1 (25%)	0.13
18-65 years	10 (33.3%)	3 (75%)	
Gender			
Male	15 (50%)	4 (100%)	0.032*
Female	15 (50%)	0	
Diagnosis			
Tumor	6 (20%)	0	0.14
Post Trauma	4 (13.3%)	1 (25%)	
Intraventricular Bleed	1 (3.3%)	1 (25%)	
Congenital Hydrocephalus	18 (60%)	2 (50%)	
Normal Pressure Hydrocephalus	1(3.3%)	0	
Co-morbidities			
Diabetic Mellitus	5 (16.7%)	1 (25%)	0.63
Type of Device			
Extra-Ventricular Drain	5 (16.7%)	1 (25%)	0.63
Ventriculoperitoneal Shunt	25 (83.3%)	3(75%)	
CSF Protein>100mg/dl	18 (60%)	3 (75%)	0.51
Type of bacteria in CSF:			0.80
No Growth	02(6.7%)	0	
Gram Positive	12 (40%)	01 (25%)	
Gram Negative	12 (40%)	02 (50%)	
	04 (13.3%)	01 (25%)	
Multidrug resistant gram negative (n=15):			
CRE	07 (46.7%)		0.34
CRA	05 (33.3%)	02 (66.7%)	
DTR-PA	03 (20%)	01 (33.3%)	
Positive Blood Culture:			
Negative	26 (86.6%)	4 (100%)	
Pseudomonas Aeruginosa	02 (6.7%)	0	0.70
Coagulase negative Staphylococcus	02 (6.7%)	0	
Symptoms:			0.69
Fever	29 (96.7%)	4 (100%)	
Catheter Management:			
• Immediate removal of VP shunt or EVD with revision.	4 (13.3%)	3 (75%)	0.001*
	12 (40%)	0	
• Exteriorization of distal end alone.	10 (33.3%)	1 (25%)	

• Exteriorization of distal end followed by VP shunt removal. VP and EVD not removed with conservative management alone.	4 (13.3%)	0	
ICU admission	17 (56.7%)	4 (100%)	0.06
Sepsis	5 (16.7%)	2 (50%)	0.055*
Mechanical Ventilation	11 (36.7%)	3 (75%)	0.87

1. CRE carbapenem resistant Enterobacterales
2. CRA carbapenem resistant *Acinetobacter*
3. "difficult-to-treat" *Pseudomonas aeruginosa* defined as isolates testing intermediate or resistant to all reported carbapenems, beta-lactams, fluoroquinolones and monobactam

DISCUSSION

Healthcare associated ventriculitis and meningitis is associated with significant mortality and morbidity. We reported a mortality rate of 13%. C Srihawan *et al* reported an overall mortality rate of 9.3% and adverse outcomes in 78% of patients.[10]

We found that male sex and sepsis were predictors of mortality in our patients with HAVM. Prior studies have reported factors associated with mortality. In a study by Rodriguez Guardado *et al*, of 51 patients with EVD-related *Acinetobacter* meningitis, 17 died from the infection. They found that lack of removal of intraventricular catheters, high CSF pleocytosis (4988.35 vs 1341 cells/mm3), and older age (50 vs 40 years) were significantly associated with mortality.[11] However, Kim *et al* did not report similar factors associated with mortality in their study of 27 patients with *Acinetobacter* meningitis.[12] Srihiwan C *et al* identified age ≥45 years, abnormal neurological exam, and mechanical ventilation as poor prognostic factors. In their study, CSF parameters and removal of intraventricular catheters were not associated with adverse outcomes, as was also demonstrated in our study.[10]

We had equal proportion of gram positive and gram-negative bacteria isolated in CSF cultures of our patients with HAVM. *Staphylococcus aureus* was the most frequently encountered pathogen, found in 53.3% of the cases in a pediatric study of shunt infections.[13] Yakut N *et al* reported that in 148 out of 290 VPS infections, coagulase negative staphylococcus was isolated in 42.5%, *Pseudomonas aeruginosa* in 14.9%, *Klebsiella pneumoniae* in 10.1% and *Staphylococcus aureus* in 10.1% of cases.[14]

Of great concern is that half of our patients had highly resistant gram negatives isolated from the CSF, which included Enterobacterales, *Acinetobacter spp*. and *Pseudomonas aeruginosa*, all of which were resistant to the carbapenems. This has implications for empirical therapy for HAVM, which should be guided by the antibiogram of the institution. In our facility, based on the findings of this study, empirical therapy for HAVM with meropenem alone, without colistin, for gram negative coverage is no longer a viable option. Colistin has limited penetration into the cerebrospinal fluid and therefore it is recommended to additionally administer intrathecal and intra-ventricular colistin for the treatment of CNS infections.[15]

In a retrospective analysis by Chen *et al*, 28 patients who had MDRO gram negative CNS infection were treated with intraventricular polymyxin B supplemented by continuous external ventricular drainage. The duration of treatment was 14.96 ± 4.28 days and negative CSF culture were achieved by 8.23 ± 4.02 days. They found a bacterial clearance rate from cerebrospinal fluid of 92.9% (26/28) with a clinical cure rate of 82.1% (23/28), thus concluding that intraventricular polymyxin B supplemented by continuous external ventricular drainage is a safe and effective treatment strategy for MDRO gram negative CNS infection. [16]

Several β-lactam/β-lactamase inhibitors (BLBLIs) have been developed for the treatment of pneumonia, urinary tract, intra-abdominal and bloodstream infections due to carbapenem-resistant Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. These include ceftolozane-tazobactam, ceftazidime-avibactam and cefiderocol as well as meropenem-vaborbactam, and imipenem-relebactam. However, there is limited data for the use of these agents in CNS infections.

Guidelines for management of HAVM recommend immediate removal of the catheter . [(17)]However, Brown *et al* treated 43 of 122 patients with CSF shunt infections conservatively with intraventricular and systemic antibiotics. The study reported that 84% of these patients were cured. A 92% success rate was reported in infections caused by bacteria other than *Staphylococcus aureus*, and included 30 patients with coagulase-negative staphylococcal infections .[(18)] This treatment approach cannot be recommended for more virulent pathogens such as gram negative and *S. aureus*. In our study, over half of the patients did not have removal of the device. None of these patients received intrathecal

or intraventricular colistin. We were not able to follow patients after discharge, and therefore cannot comment on the long-term success of conservative management. Limitations of our study is that it is a single-center retrospective study and the number of cases is relatively small. Moreover, the study design was unable to incorporate follow-up of patients after discharge, which is logistically challenging at the Trauma Institute since patients are discharged back to referring healthcare facilities that are often located in distant towns or provinces.

CONCLUSION

This retrospective, single center study examined 30 patients with healthcare associated ventriculitis and meningitis. Male sex and sepsis were found to be predictors for mortality. Cerebrospinal cultures demonstrated equal representation of gram positive and gram-negative bacteria. Almost all gram negatives isolated were resistant to the carbapenems, which is challenging to treat due to limited antimicrobial options. A prospective study with larger sample size is recommended for further analysis of clinical characteristics, microbiology, outcome and risk factors for mortality and morbidity in patients with HAVM.

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Nazish Arshad: Conception, frame work, literature search, data interpretation and drafting, accountable for all aspects of the work

Saima Samad: Data collection, data Analysis, accountable for all aspects of the work

Sughand Memon: Literature search, accountable for all aspects of the work

Sadia Ishaque: Review of manuscript, accountable for all aspects of the work

Shehla Baqi: Study design, critical review, final approval of the article, accountable for all aspects of the work

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