

Impact of Antibiotic Therapy in the Microbiological Yield of Healthcare-Associated Ventriculitis and Meningitis

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The impact of antibiotic therapy on the diagnosis of healthcare-associated ventriculitis and meningitis (HCAVM) is unknown. Antibiotics were administered before obtaining cerebrospinal fluid (CSF) in 217 out of 326 (66%) patients with HCAVM, and they impacted the sensitivity of the cerebrospinal fluid Gram stain and culture ($P \leq .004$).

Keywords. antibiotic, CSF culture, healthcare-associated, meningitis, ventriculitis.

Infections in hospitalized patients are common, especially among neurosurgical patients [1, 2]. Healthcare-associated bacterial infections are often resistant to a wide range of antibiotics and are often associated with high morbidity and mortality [1–3]. Healthcare-associated ventriculitis and meningitis (HCAVM) is associated with adverse clinical outcomes in the majority of patients and represents an independent prognostic factor of an adverse clinical outcome in neurosurgical patients [4–6]. Patients with suspected HCAVM can present diagnostic dilemmas due to the low sensitivity of the cerebrospinal fluid (CSF) Gram stain (20%) and cultures (50%) [4]. Often, patients receive antibiotics before the collection of CSF, which could potentially affect the yield of the culture [2]. Further, neurosurgical patients such as those with intracranial hemorrhage are a diagnostic challenge as they may develop a chemical meningitis, decreasing the reliability of the routine CSF profile, such as white blood cells (WBCs), protein, and glucose, in helping clinicians assess the possibility of an infection [2, 6]. Without a

causative organism identified, the diagnosis of infectious meningitis is in question, and definite therapy such as removal of neurosurgical devices can be withheld [7, 8]. The purpose of our study was to compare the clinical and laboratory characteristics of adults and children with HCAVM treated with antibiotics before CSF analysis with those who were not treated and to evaluate the impact of this treatment on microbiological confirmation. Furthermore, we explored the effect of duration of antibiotic therapy on CSF culture rates and differences in the clinical management of patients with positive vs negative CSF cultures.

METHODS

Patients age ≥ 2 months with HCAVM admitted to Memorial Hermann Hospital or Texas Children's Hospital between August 24, 2003, and July 18, 2017, were eligible, and prospective candidates were identified using International Classification of Diseases (ICD) 9 coding. HCAVM was further defined using the National Hospital Surveillance Network (NHSN)/Centers for Disease Control and Prevention (CDC) criteria [9]. Adult patients must meet at least 1 of the following criteria:

- an organism identified from CSF by a culture- or non-culture-based microbiologic testing method;
- at least 2 of the following symptoms or signs:
 - a) fever or headache,
 - b) meningeal signs,
 - c) cranial nerve signs.

And at least 1 of the following:

- a) abnormal CSF analysis (increased white blood cells, elevated protein, and decreased glucose);
- b) organism seen on Gram stain of CSF;
- c) organism identified from blood by a culture- or non-culture-based microbiologic method;
- d) diagnostic single-antibody titer (IgM) or 4-fold increase in paired (IgG) for organism.

Patients ≤ 1 year of age had similar criteria, with the exception that symptoms and signs were different:

- fever, hypothermia, apnea, bradycardia, or irritability;
- meningeal signs;
- cranial nerve signs.

Clinical outcomes were assessed via the Glasgow outcome scale at the time of discharge, and an adverse clinical outcome was categorized as a Glasgow outcome scale from 1 to 4 [4].

Data were collected at the time CSF was obtained. Patients without CSF analysis were excluded from the study. CSF was

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obtained either via lumbar puncture or by accessing the intraventricular device. Patients without an intraventricular device were assessed via a lumbar puncture, and those with either a lumbar drain or ventriculoperitoneal (VP) shunt were assessed by aspiration from the device. Cultures were held for 5 days and then discontinued if they showed no signs of growth. Any patient who received antibiotic treatment for any length of time in their hospitalization before the diagnostic lumbar puncture was considered in the antibiotic pretreatment group. Statistical analysis was run using IBM SPSS, version 25, using the analysis of variance test for continuous data and chi-square test and Fisher exact tests for bivariate data analyses.

RESULTS

A total of 326 adults and children with HCAVM were identified, with antibiotics being administered to 217 (66%) patients (Table 1). There was no statistically significant difference in age, intensive care unit (ICU) admission, or mechanical ventilation in those patients receiving antibiotic therapy before the CSF analysis vs those who did not receive antibiotics ($P > .2$). Pretreatment with antibiotics significantly reduced the sensitivity of the CSF Gram stain (25.7% vs 13.4%, $P = .003$) and

CSF culture (66.1% vs 48.5%, $P = .004$) but had no impact on the yield of blood cultures ($P = .716$). Furthermore, antibiotic therapy had no impact on CSF or serum WBC counts, CSF red blood cell, CSF protein, CSF glucose, or CSF lactate levels ($P > .5$). Administration of antibiotics before CSF acquisition did not impact the likelihood of an adverse clinical outcome, as measured on the Glasgow outcome scale (70.6% vs 78.3%, $P = .173$).

Of the 326 patients, 178 (54%) had a positive CSF culture (Table 1). We found no differences between patients with culture-positive and culture-negative HCAVM with regards to gender, race, age, comorbidity status, immune status, CSF Gram stain results, CSF protein level, CSF glucose level, CSF leak, ICU admission, Glasgow coma score, focal neurological exam rates, stiff neck, nausea and vomiting, or use of mechanical ventilation that may have influenced the probability of receiving antimicrobial administration before their lumbar puncture ($P > .05$) (data not shown). A total of 259 patients (79%) had a neurological device; those with a lumbar drain (LD) were more likely to have a positive CSF culture than those with an external ventricular device or a ventriculoperitoneal shunt (68% vs 53% and 54%, respectively, $P = .039$). There was no difference in the rate of removal of devices in those patients with a positive or a negative CSF culture (80.4% vs 81.9%, respectively, $P = .771$).

Table 1. Pretreatment With Antibiotics Before Cerebrospinal Fluid Testing and Management in 326 Adults and Children With Healthcare-Associated Ventriculitis and Meningitis

	No Pretreatment (n = 109)	Pretreated (n = 217)	P Value
Age ^a	49 y (2 mo–86 y)	48 years (2 mo–87 y)	.546
ICU admission	93 (85.3)	190 (87.6)	.312
Mechanical ventilation	52 (47.7)	108 (49.8)	.636
Positive CSF Gram stain	28 (25.7)	29 (13.4)	.003
Positive blood culture	10/95 (10.5)	18/196 (9.2)	.716
Positive CSF culture	72 (66.1)	106 (48.5)	.004
CSF protein, mg/dL	154 (9–5667)	157.5 (16–6000)	.579
CSF glucose, mg/dL	51 (1–184)	46 (1–221)	.892
CSF WBC	290 (0–29 000)	426.5 (0–960 000)	.413
CSF RBC	1525 (0–600 000)	1812.5 (0–3 980 000)	.470
Serum WBC	12.9 (0.26–48.7)	13.8 (4.8–42.1)	.201
CSF lactate	4.50 (1.9–22.8)	4.65 (1.0–13.8)	.098
Adverse clinical outcome ^a	77 (70.6)	170 (78.3)	.173
Management by CSF culture results	Positive CSF Culture (n = 178) ^b	Negative CSF Culture (n = 148)	P Value
Length of stay, d	23 (3–130)	22 (1–128)	.750
CNS device removed ^{c,d}	90/112 (80.4)	86/105 (81.9)	.771
Duration of antibiotic therapy, d	14 (1–288)	14 (0–63)	.043
Time from antibiotic treatment to LP ^e , h	24 (1–168)	48 (1–168)	.052

Values are presented as median (range) or No. (%).

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; ICU, intensive care unit; LP, lumbar puncture; RBC, red blood cell count; WBC, white blood cell count.

^aAdverse clinical outcome is defined as a Glasgow outcome scale 1–4.

^bCSF cultures were positive for Gram-positive bacteria (94): *Staphylococcus aureus* (35); coagulase-negative staphylococcus (21); *Enterococcus faecalis* (3); alpha-hemolytic streptococcus (13); *Streptococcus pneumoniae* (4); *Streptococcus agalactiae* (3); *Bacillus cereus* (3); *Corynebacterium* spp. (2); nontuberculous mycobacteria (2); micrococcus (1); *Propionibacterium* spp. (1); and for Gram-negative bacteria (84): *Pseudomonas aeruginosa* (20); *Escherichia coli* (18); *Klebsiella pneumoniae* (14); *Enterobacter cloacae* (13); *Serratia marcescens* (12); *Enterobacter aerogenes* (12); *Acinetobacter baumannii* (3); *Haemophilus influenzae* (2); *Chryseobacterium* spp. (1); *Stenotrophomonas maltophilia* (1).

^cData available for 217/259 (84%) patients with devices.

^dTypes of devices (CSF culture positive/CSF culture negative by type of device: external ventricular devices [90/170, 53%]; lumbar shunts [35/51, 53%]; ventriculoperitoneal or ventriculoatrial shunts [21/38, 54%]; $P = .039$); CSF obtained from an EVD was more likely to have a positive CSF culture than CSF obtained through lumbar puncture (57% vs 41.5%, $P = .37$).

^ePatients treated for less than 24 hours were more likely to have a positive CSF culture (64% vs 42%, $P = .037$).

Even though the duration of antibiotic therapy was longer in those with a positive CSF culture vs negative CSF culture (median [range], 14 [1–288] vs 14 [0–63] days, $P = .43$), there was no difference in length of stay (23 vs 22 days, $P = .750$). There was a statistical trend toward a shorter duration of antibiotic exposure before obtaining the CSF in those with a positive culture (24 hours in culture positive vs 48 hours in culture negative, $P = .052$). In further analysis, patients treated for less than 24 hours were more likely to have a positive CSF culture (64% vs 42%, $P = .037$).

DISCUSSION

To the best of our knowledge, this is the first study to examine the impact of antibiotic therapy and its duration on the yield of microbiological methods in adults and children with HCAVM. Not surprisingly and similar to community-acquired bacterial meningitis in children [10], pretreatment with antibiotic therapy and its duration (>24 hours) further reduce the already low sensitivity of the CSF culture in HCAVM [4]. This is problematic as it affects confirmatory evidence for the diagnosis of HCAVM, impacting the ability to adjust empirical antibiotic therapy to a narrower range of agents. Furthermore, the lack of culture confirmation may affect the recommendation of the removal of infected neurosurgical devices, even though in this study there was no difference in the rate of removal between those with a positive vs negative culture [2, 8]. In the absence of a positive CSF Gram stain or culture, the diagnostic accuracy of the CSF profile and markers in neurosurgical patients are of limited value, suggesting chemical meningitis instead [2, 8].

Our study, as also seen in pediatric community-acquired bacterial meningitis [10], shows no impact of pretreatment with antibiotic therapy on CSF profiles such as WBC, protein, glucose, and lactate levels. This is important as clinicians can still rely on the CSF profile to assess the possibility of infectious vs chemical meningitis in a particular neurosurgical patient. A recent clinical model has been derived but not validated that uses several markers (C-reactive protein, CSF/blood glucose ratio, CSF granulocytes, and CSF lactate) to help calculate the possibility of postoperative meningitis [11].

The administration of antibiotics before lumbar puncture was not associated with an improvement in clinical outcomes. This contrasts with studies of adults with community-acquired bacterial meningitis, where a delay in empirical antibiotic therapy is associated with worse clinical outcomes [12]. This may be due to the fact that many of these patients already have neurological deficits from the primary neurosurgical diagnosis or therapy that followed.

There was no difference in the proportion of CNS devices that were removed between those patients with and without a positive CSF culture. This is most likely due to the fact that the majority of the CNS devices in this study had temporary

external ventricular devices or lumbar drainages that were removed when infection was suspected.

Our study has several strengths. It is the first study to our knowledge that has evaluated the impact of antibiotic therapy and its duration on the yield of microbiological studies in HCAVM. Second, our study is large and includes both adults and children from 2 large tertiary care referral centers. Third, the study utilized the NHSN/CDC criteria to diagnose patients with HCAVM, which are used by several infection control departments in the United States. Lastly, this is the first study to evaluate the impact of CSF culture positivity on CNS device removal. This study, however, did have some limitations. First, the study was done in Houston, Texas, and needs to be validated by other studies in different geographical areas. Second, decisions to start empiric antibiotic therapy before CSF sampling were made by the treating physicians, and this could introduce propensity bias. Third, guidelines for the management of these patients were not uniformly followed and changed during the study time frame, so management decisions based on these guidelines likely changed as well. Finally, the CSF cultures were only kept for 3–5 days for the majority of patients, preventing the detection for fastidious organisms such as *Propionibacterium acnes*.

CONCLUSIONS

Adults and children with HCAVM who received antibiotic treatment before obtaining CSF studies had statistically significantly lower rates of positive CSF Gram stain and culture but experienced no difference in CSF profile or clinical outcomes. Antibiotic treatment can affect the ability to confirm the diagnosis of HCAVM and should be withheld if possible until after obtaining the CSF studies.

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