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Factors affecting in-hospital mortality and outcome study on healthcare-associated meningitis and/or ventriculitis (HCAMV): University of Malaya Medical Centre experience

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Abstract

Background & Objectives: Healthcare-associated Meningitis and/or Ventriculitis (HCAMV) is a serious yet frequent complication following neurosurgery. In this study, the clinical outcomes of HCAMV, risk factors associated with the clinical outcome, etiological agents and their corresponding antibiogram were investigated. *Methods:* All HCAMV patients treated in University Malaya Medical Centre (UMMC) from 2012-2017 were retrospectively reviewed. The inclusion criteria were 1) adult patient of 18 years of age and above, 2) positive CSF culture and 3) diagnosed as HCAMV after neurosurgical procedure. Patients' clinical data, etiological agents and the antibiogram of HCAMV were recorded. Patients were interviewed via phone to assess neurological deficit post-discharge. Clinical outcomes were Glasgow Coma Scale (GCS) during onset of HCAMV, patient's mortality, and post-discharge modified Rankin Scale (mRS). *Results:* Fifty two subjects were included in our study and male subjects predominated (65.4%, n=34) with the median age of 53 years old (range 20-75). Close to half of them had severe GCS (46.2%, n=24) and were intubated (48.1%, n=25). In regard to organisms recovered from the CSF, Gram-negative bacteria predominated (59.6%, n=31). Of these *Acinetobacter baumannii* was the commonest (38.5%, n=20) and carbapenem resistance was documented in 75% (n=15) of *Acinetobacter baumannii*. In-hospital mortality rate was 32.7% (n=17) and additional 20 subjects died within a year of HCAMV diagnosis. Multivariate analysis showed intubation associated with in-hospital mortality in this study (aOR, 0.3; P = 0.001).
Conclusion: We reported a high percentage of HCAMV caused by carbapenem-resistant *Acinetobacter baumannii* and intubation is an independent risk factor for in-hospital mortality.

Keywords: Meningitis, ventriculitis, post neurosurgical infection, carbapenem resistant *Acinetobacter baumannii*

INTRODUCTION

Meningitis and/or ventriculitis are not only community acquired, but also nosocomial in onset due to healthcare-associated meningitis and/or ventriculitis (HCAMV) following invasive neurosurgical procedures in both head trauma cases and brain tumour removal.[1,2] The incidence of HCAMV varies between 5%-20% as reported previously.[3-7] Differing etiological agents have been reported from various cohorts and patient population.[1,2,8-10]

The classical signs and symptoms of HCAMV are new onset of headache, fever, evidence of meningeal irritation, seizure and/or worsening of mental status[1]. However, such symptom-based approach might not have a good sensitivity in HCAMV diagnosis as patients are likely to have lower admission Glasgow Coma Scale (GCS) and be intubated.[11] Thus, true incidence and burden of HCAMV may be different from the reports in the literature.[1,12-14]

Difficulty in diagnosing HCAMV can lead to delayed antimicrobial therapy. Moreover, HCAMV is commonly caused by multidrug resistant organisms[15], which can drive the rates of initial appropriate antibiotic therapy down as the empiric regimens are inactive against the

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organisms. These are associated with a number of serious consequences including an increased risk of mortality.[14,16] Mortality rate associated with treatment failure ranged from 20-50% as demonstrated in previous studies.[1,16] Therefore, an early and accurate diagnosis is crucial for post-neurosurgery HCAMV. Detection of true infection can be improved by using reliable investigation such as CSF analysis.[1,17]

Despite tremendous amount of research dedicated in the field of healthcare-associated infection, little effort had been devoted in investigating the clinical outcomes and the factors associated with them in the developing world, such as Malaysia. Hence, this study aims to investigate the clinical outcomes of post-neurosurgical HCAMV among adults who were admitted to University Malaya Medical Centre (UMMC). Our primary outcomes were 1) in-hospital as well as 1 year-mortality rates. Our secondary outcomes were to analyse 1) the risk factors associated with the clinical outcomes above, 2) etiological agents of HCAMV and 3) the corresponding antibiogram of these agents.

METHODS

Identification of patient and data collection

This retrospective study aims to investigate all adult patients with culture proven HCAMV treated in UMMC from the year 2012 to 2017. This study was approved by the institutional ethical board. (MREC: 201768-5332). Microbiology intranet system was used to capture possible candidates for our study by screening all CSF samples received by the laboratory within the stipulated period above from neuro ICU wards. Patients who met our inclusion criteria were recruited into the study.

Our inclusion criteria were 1) adult patient ≥18 years, 2) positive CSF culture and 3) diagnosed as HCAMV after neurosurgical procedure. We excluded patients who did not meet any of the above criteria. A standardized case report form (CRF) was used to capture all the relevant data, which included types of neurosurgical procedure that the subjects underwent, their co-morbidities, immune-compromising state and immune-suppressive treatment (e.g. steroid therapy within 3 months of presentation) that subjects received prior to HCAMV diagnosis. The following was collected in addition; the documented clinical presentation of HCAMV during its onset, laboratory parameters, empirical antibiotics prescriptive pattern and the outcomes of the study subjects. Carbapenem-resistant *Acinetobacter baumannii* was defined as the isolate that is non-susceptible to at least one carbapenem antibiotic.

The diagnosis of HCAMV was based on Infectious Diseases Society of America (IDSA) 2017 guideline[1] and was defined as positive CSF culture for bacterial pathogen (s) in a patient who had; (1) clinical features of meningitis (i.e. fever, altered consciousness, seizures, acute hydrocephalus and signs of meningeal irritation), (2) purulent CSF features, with at least one of the following: i) pleocytosis with leukocyte count >0.25 mmol/L and predominant polymorphonuclear cells, ii) lactate concentration >3.5 mmol/L, iii) hypoglycorrhachia as evidenced by glucose ratio (CSF glucose/serum glucose) < 0.4 or CSF glucose level ≤ 2.5 mmol/L if no simultaneous blood glucose level was determined.

The severity of neurological deficits during the onset of HCAMV of the subjects were defined using Glasgow Coma Scale (GCS). Severe deficit was defined as GCS ≤8, moderate deficit as GCS between 9 and 12, whereas mild deficit as GCS 13 to 15.

Any subjects who were discharged following HCAMV were interviewed via phone using a multi-language standardised questionnaire and modified Rankin Scale (mRS)[18] to assess their neurological deficit for their outcome. Subjects who did not have mortality data or could not be contacted during the phone-call interview were censored from clinical outcome observation.

Statistical Analysis & sample size calculation

Statistical analysis was performed using SPSS version 25. All the patients who fulfilled the criteria above was included into this study. Chi-square test or Fisher's exact test was used for categorical variables and independent Student's t-test for normally distributed continuous variables, and Mann-Whitney test for nonnormally distributed continuous variables. Multivariate cox-regression analysis (forward stepwise method) was also used to identify the risk factors associated with in-hospital mortality taking into consideration date of admission and the onset of HCAMV of the patients can vary in the cohort. A statistically significant result was defined as a test showing a $P<0.05$.

RESULTS

Fifty-two adults were included in our study and male subjects predominate (65.4%, n=34) with the median age of 53 years old (range 20-75). Close to half were hypertensive (48.1%, n=25) and

14 had an underlying malignancy (26.9%). The commonest symptoms were fever (61.5%, n= 32) followed by seizure and headache (11.5%, n=6 and 9.6%, n=5 respectively). The details of patients' demographics as well as their clinical features are demonstrated in Table 1. In terms of neurosurgical procedures performed, more than half were carried out as emergency surgeries (53.8%, n=28). When looking at all the procedures, 59.6%, (n=31) were CSF diversion procedure, 32.7%, (n=17) were cranial work procedure and the remainder were coiling procedure (n=1), wound debridement (n=1) and tumour excision (n=2). Among all CSF diversion procedures, majority were external ventricular drains (n=26, 83.9%) followed by ventriculo-peritoneal (VP) shunts (16.1%, n=5). Three types of cranial work procedures were performed: craniectomy (13.5%, n=7), craniotomy (13.5%, n=7), and burr-holes (3.8%, n=2). Non traumatic insults were the commonest indication for these procedures. (92.3%, n=48).

Table 1: Clinical characteristics of HCAMV

Comorbidities	
ESRD	(1.9%, n=1)
Diabetes Mellitus	(21.2%, n=11)
Hypertension	(48.1%, n=25)
Stroke	(9.6%, n=5)
Malignancy	(26.9%, n=14)
COPD	(1.9%, n=1)
Asthma	(1.9%, n=1)
Ischemic Heart Disease	(3.8%, n=2)
Others	(25.0%, n=13)
Clinical Features	
Headache	(9.6%, n=5)
Fever	(61.5%, n=32)
Neck stiffness	(1.9%, n=1)
Seizure	(11.5%, n=6)
Altered mental status	(26.9%, n=14)
Mild GCS	(28.8%, n=15)
Moderate GCS	(25.0%, n=13)
Severe GCS	(46.2%, n=24)
Intubation	(48.1%, n=25)
Complications	
Hydrocephalus	(23.1%, n=12)
Shock	(5.8%, n=3)
Others	(30.8%, n=16)

HCAMV-healthcare-associated meningitis and/or ventriculitis, ESRD-end stage renal disease, COPD-chronic obstructive pulmonary disease, GCS-Glasgow Coma Scale.

Assessment of neurological deficit showed close to half had severe neurological deficit (46.2%, n=24) and the rest had mild (28.8%, n=15) and moderate deficit (25.0%, n=13). Close to half were also intubated (48.1%, n=25) and 12 (23.1%) were complicated by hydrocephalus. Majority of the subjects had CSF analysis performed at baseline (98.1%, n=51) and of these, 64.7% (n=33) showed CSF abnormalities which were suggestive of infection. The most common abnormalities were increased CSF protein (92.2%, n=47) and pleocytosis (92.2%, n=47), followed by hypoglycorrhachia (62.7%, n=32).

Gram-negative bacteria (GNB) predominated (59.6%, n=31) with the remainder being Gram-positive bacteria (GPB) (40.4%, n=21). Of these *Acinetobacter baumannii* was the commonest (64.5%, n=20) for GNB, whereas for GPB, coagulase negative staphylococcus (CoNS) (61.95%, n=13) predominated, followed by *Staphylococcus aureus* (28.6%, n=6). In terms of antibiotic susceptibility pattern, carbapenem resistance was documented in 75% (n=15) of *Acinetobacter baumannii*. Methicillin resistance was detected in half (50.0%, n=3) of *S. aureus* isolates, with a higher rate seen for CoNS at 84.6% (n=11) (Table 2).

In-hospital mortality rate for our cohort was 32.7% (n=17) and additional 20 subjects died within a year of HCAMV diagnosis. Of note, 7 subjects were uncontactable for mortality assessment. The survivors who were followed up (48.1%, n=25) had mean survival duration of 29.56 months (range 7 to 56 months) post discharge and 8 out of 25 patients had mRS of 6 (died) in 2 years follow up from onset of infection (Table 3). For risk factors associated with in-hospital mortality, severe GCS impairment, intubation, CoNS as HCAMV aetiology and CSF hypoglycorrhachia were significant variables in univariate analysis. In multivariate analysis, only intubation remains a significant risk factor. The details of these are shown in Table 4.

DISCUSSION

HCAMV is a rare but serious complication of neurosurgical procedures[8]. However, data on this is scarce from developing countries leading to a possible underestimation of its true burden and impact.[19,20] Additionally, there is a strong trend of antibiotic resistance in these regions based on

Table 2: Result of CSF culture and the antibiotic resistance profile

Organism	Antibiotic resistance	n (%)
Gram-Positive bacteria		21
Staphylococcus aureus	Total	6
	Methicillin resistance	3 (50%)
	Methicillin sensitive	3 (50%)
Coagulase Negative Staphylococcus	Total	13 (25.0%)
	Methicillin resistance	11 (84.6%)
	Methicillin sensitive	2 (15.38%)
Streptococcus pneumoniae	Total	1 (1.9%)
	Penicillin resistance	0 (0.0%)
	Penicillin sensitive	1 (100.0%)
Enterococcus faecium	Total	1 (1.9%)
	Ampicillin/ Penicillin resistance	1 (100.0%)
	Ampicillin/ Penicillin sensitivity	0(0.0%)
	Vancomycin resistance	0 (0.0%)
	Vancomycin sensitive	1 (100.0%)
Gram-negative Bacteria		31 (59.6%)
Klebsiella pneumoniae	Total	3 (5.8%)
	Amoxicillin-clavulanic acid resistance	2 (66.7%)
	Ampicillin resistance	3 (100.0%)
	Amikacin resistance	1 (33.3%)
	Ciprofloxacin resistance	1 (33.3%)
	Ceftriaxone resistance	3 (100.0%)
	Cefotaxime resistance	3 (100.0%)
	Cefuroxime resistance	3 (100.0%)
	Ertapenem resistance	1 (33.3%)
	Cefepime resistance	3 (100.0%)
	Gentamicin resistance	2 (66.7%)
	Imipenem resistance	1 (33.3%)
	Meropenem resistance	1 (33.3%)
	Ampicillin-sulbactam resistance	3 (100.0%)
	Trimethoprim-sulfamethoxazole resistance	2 (66.7%)
	Piperacillin-tazobactam resistance	2 (66.7%)
Enterobacter sp.	Total	1 (1.9%)
	Cefepime resistance	0 (0.0%)
	Imipenem resistance	0 (0.0%)
	Meropenem resistance	0 (0.0%)
	Ertapenem resistance	0 (0.0%)
Serratia marcescens	Total	2 (3.8%)
	Cefepime resistance	0 (0.0%)
	Imipenem resistance	0 (0.0%)
	Meropenem resistance	0 (0.0%)
	Ertapenem resistance	0 (0.0%)

Organism	Antibiotic resistance	n (%)
Acinetobacter baumannii	Total	20 (38.5%)
	Ceftazidime resistance	15 (75.0%)
	Cefepime resistance	15 (75.0%)
	Ertapenem resistance	8 (40.0%)
	Imipenem resistance	15 (75.0%)
	Meropenem resistance	15 (75.0%)
	Gentamicin resistance	10 (50.0%)
	Piperacillin-tazobactam resistance	15 (75.0%)
Pseudomonas aeruginosa	Total	3 (5.8)
	Ceftazidime resistance	0 (0.0%)
	Cefepime resistance	0 (0.0%)
	Ertapenem resistance	0 (0.0%)
	Imipenem resistance	0 (0.0%)
	Meropenem resistance	0 (0.0%)
	Gentamicin resistance	0 (0.0%)
Haemophilus influenzae	Total	2 (3.8%)
	Ceftriaxone resistance	1 (50.0%)
	Cefotaxime resistance	1 (50.0%)

CSF-cerebrospinal fluid

multiple cohorts and sentinel data.[21-24] Our cohort showed comparable incidence of HCAMV as well as preceding operations and brain insults prior to HCAMV onset. In a large multicentre study in Hong Kong involving 538 patients, traumatic brain injury, emergency shunting as well as lone-vancomycin prophylactic strategy preceded its onset and were reported as risks for HCAMV.[25] Similarly, previous head surgeries such as revision of shunt for mechanical dysfunction, the time of the day that an operation was carried out (i.e. surgery that commenced after 10 am) and prolonged operating time carries significant risks for infection.[26]

Recently, there is an increase in the incidence of carbapenem-resistant *Acinetobacter baumannii* (CRAB) reported worldwide especially in the East and South East Asia region.[27] In a review by Hsu *et al*. more than half of *Acinetobacter baumannii* isolates recovered from patients and the hospital environment in Malaysia express such resistance.[27] Similar results were reported from a local non-teaching hospital in Northern part of Peninsular Malaysia, which showed that up to a third of HCAMV cases were caused by *Acinetobacter baumannii* and majority were carbapenem resistant (i.e. 85.7%).[21] We saw a relatively similar pattern, whereby *Acinetobacter baumannii* was our most common aetiology (38.5%, n=20) with 75% showing

Table 3: mRS of HCAMV survivors during phone call interview on average of 2 years from onset of infection

mRS	
0	(28.0%, n=7)
1	(8.0%, n=2)
2	(8.0%, n=2)
3	(0.0%, n=0)
4	(16.0%, n=4)
5	(8.0%, n=2)
6	(32.0%, n=8)

Table 4: Association between clinical characteristics and in-hospital mortality among HCAMV patients

Categorical variables	In hospital mortality, n (%)		Univariate analysis		Multivariate analysis	
			OR (95% CI)	P-value	aOR (95% CI)	P-value
	Yes	No				
Female	6 (33.3%)	12 (66.7%)	0.1 (0.3 – 3.2)	0.943[a]	-	-
VP shunt	2 (40.0%)	3 (60.0%)	0.7 (0.1- 4.7)	>0.999[b]	-	-
EVD	9 (34.6%)	17 (65.4%)	0.8 (0.3 – 2.7)	0.768[a]	-	-
Craniectomy	5 (41.7%)	7 (58.3%)	0.6 (0.2 – 2.3)	0.496[b]	-	-
Diabetes mellitus	4 (36.4%)	7 (63.6%)	1.2 (0.3 – 5.0)	>0.999[b]	-	-
Severe GCS	12 (50.0%)	12 (50.0%)	0.2 (0.1 – 0.8)	0.014[a]	-	-
Moderate GCS	4 (30.8%)	9 (69.2%)	1.1 (0.3 – 4.4)	>0.999[b]	-	-
Mild GCS*	1 (6.7%)	14 (93.3%)	10.7 (1.3 – 89.8)	0.011[b]	-	-
Intubation*	12 (48.0%)	13 (52.0%)	4.1 (1.2 – 14.2)	0.024[a]	0.3 (0.1 – 0.6)	0.001
CoNS	1 (7.7%)	12 (92.3%)	8.3 (1.0 – 70.8)	0.039[b]	-	-
Staphylococcus aureus	1 (16.7%)	5 (83.3%)	2.7 (0.3 – 24.8)	0.650[b]	-	-
Acinetobacter baumannii	9 (45.0%)	11 (55.0%)	0.4 (0.1 – 1.3)	0.135[a]	-	-

[a]=Pearson Chi-Square Test applied, [b]=Fisher's Exact Test applied, OR-Odds Ratio; CI-Confidence interval; VP shunt-ventriculo-peritoneal shunt; EVD-external ventricular drain; GCS-Glasgow Coma Scale; CoNS-coagulase negative Staphylococci, *=included in cox-regression

Continuous variables	In hospital mortality, mean (SD)		Univariate analysis		Multivariate analysis	
			t/ z	P-value	aOR (95% CI)	P-value
	Yes	No				
Age (years)*	54.5 (15.5)	50.0 (12.2)	1.2[a]	0.253[a]	-	-
CSF white cell count(cells/microL)*	3432.7 (3527.0)	3454.6 (9782.0)	-1.7[b]	0.087[b]	-	-
CSF white cell polymorph (%)*	94.4 (9.1)	81.33 (25.9)	-2.2[b]	0.028[b]	-	-
CSF Glucose concentration (mmol/L)	1.0 (1.4)	14.0 (68.4)	-2.7[b]	0.008[b]	-	-
CSF protein concentration (g/L)	3.0 (3.4)	32.0 (175.8)	-0.9[b]	0.358[b]	-	-
Serum CRP	10.1 (10.7)	6.1 (6.4)	-1.3[b]	0.187[b]	-	-
Serum ESR	61.4 (34.9)	49.4 (24.1)	-0.9[b]	0.376[b]	-	-
Serum White cell count	17.0 (7.5)	54.9 (235.8)	-1.0[b]	0.301[b]	-	-
Serum platelet count	352.8 (253.0)	349.8 (140.6)	-0.8[b]	0.447[b]	-	-

[a]=Student's t-test applied, [b]=Mann-Whitney test applied. CSF-cerebrospinal fluid; CRP-C-reactive protein; ESR-erythrocyte sedimentation rate, *=included in cox-regression

carbapenem resistance. This underlines a pressing issue faced by the healthcare system in the South Asia region in terms of empiric antibiotic choice for HCAMV. Major international guidelines recommend the use of anti-pseudomonal beta-lactams and vancomycin as the main empiric regimen for nosocomial meningitis[1]. These beta lactams include cefepime, ceftazidime and meropenem and none of these are active against CRAB. Complicating this matter would be our to-go-to agent for CRAB management, which is polymyxins.[15] These agents are both nephrotoxic and neurotoxic with erratic pharmacokinetic behaviour. They have poor penetration into the blood brain barrier, which necessitates the use of intrathecal dosing.[15] It is unclear currently whether an empiric use of both systemic and locally administered polymyxins in HCAMV is safe and efficacious.[1]

Variable rates of mortality have been reported following HCAMV in the literature. Wang *et al*. reported an overall mortality rate of 22.0% in the first period of a 16-year-long study and 36.0% in the second half.[28] In another study, an overall mortality of 16.5% involving 91 cases of HCAMV was reported.[29] We demonstrated a higher in-hospital mortality rate of 32.7% and 1-year mortality rate of 38.5% in our cohort. Our rate is comparable to a report sourced from Korea that looked only at *Acinetobacter baumanii* HCAMV.[30] The death rate following meningitis was 38.9% in this report and carbapenem resistance was shown to be a significant driver for this. Higher rates have been reported in other cohorts ranging from 55% to 65%.[21,31,32] This may reflect the impact of carbapenem-resistance in driving the mortality rate up as the initial therapy could be ineffective against these organisms. There are other possible drivers for mortality in HCAMV and this includes the lack of removal of intraventricular catheters, the use of steroid, *P. aeruginosa* infection, polymicrobial infection, lower GCS, and a longer duration the EVD was in place before the diagnosis of VRI were related with higher mortality.[21,30] Of note, a previous study by Srihawan *et al*. demonstrated that mechanical ventilation was associated with adverse outcome in HCAMV patients, similar to our findings.[30]

This study is not without limitations. First, the retrospective nature of this study and second, our small sample size, which provides us with low statistical power for analysis. Furthermore, assessment of 1-year mortality was limited by the rate of returned call and resulted in further contraction of the sample size due to non-response.

In conclusion, we reported a high percentage of HCAMV caused by CRAB and intubation is an independent risk factor for in hospital mortality.

DISCLOSURE

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