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EDITORIAL

BIG BANG

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We hope to end the year 2019 with a big bang by coming out with this issue to keep our journal on track with our releases. Indeed, a big bang as each issue comes out from nothing and the forces joined and stars aligned that we are now coming out with an issue with several original articles, a case series and a feature article.

2019 is an "Infectious Year." A year when we were optimistic that great strides in ID will be seen and felt, instead we here in the Philippines had one outbreak to the next- from measles to dengue. A year when we had the re-emergence of the dreaded polio. A year when rise in HIV cases is unprecedented. We have not wavered though. We are staunch advocates, living by our oath and finding all means to protect children from dreaded infectious diseases.

While Big Bang mainly refers to the cosmic explosion or is associated with the banking and finance event in 1986, it could very well mean any sudden forceful beginning or a radical change. We at the PIDSP Journal are hopeful that the coming years will bring about a positive radical change in the landscape of Pediatric Infectious Diseases from keeping up with the technology to spread our advocacies #vaccinesavelives, to learning via the online platform, to getting hold of newer ID diagnostic tests and furthering research to answer more questions. On our journal's journey, we hope for a forceful beginning in 2020 as we aspire for our lofty goals to give our readers valuable information and sound scientific data put out on time one issue at a time.

FEATURE ARTICLE

VACCINE TRUST AS A PUBLIC TRUST

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In September 2019, the Department of Health declared a polio outbreak after two cases of the paralyzing disease were confirmed in the country. After outbreaks of measles and dengue in the same year, another outbreak of a vaccine-preventable disease has once again put into sharp focus the declining vaccination rates in the Philippines. Declining rates of vaccination have already been a problem in the country, but this has been exacerbated by the Dengvaxia controversy that further pushed the vaccination rates down. The re-emergence of polio, after being a polio-free country for 19 years, presents another opportunity to address issues in vaccine trust.

The Philippines was already deemed at-risk of having a polio outbreak due to persistently low polio vaccination rates, sub-optimal performance of acute flaccid paralysis surveillance and poor hygiene conditions. The current outbreak – now with 8 cases – is the result of the above risks factors, especially chronic under-vaccination that allowed the emergence of mutated vaccine-derived polio virus (VDPV) strains that caused the confirmed cases of disease. In response, the DOH has implemented a massive program of supplemental immunization activities (SIA) in affected regions. Other government agencies and private organizations have given their support to the SIA as well. But beyond the outbreak response, the root causes of low vaccination rates should be addressed by all stakeholders.

Vaccine hesitancy has been described by the World Health Organization as a 2019 top global health threat. Addressing vaccine hesitancy and restoring trust in vaccines are thus paramount goals in obtaining health for all. Improving health communication skills is a key step in tackling this. In the report mentioned above, the WHO also states that "*health workers, especially those in*

communities, remain the most trusted advisor and influencer of vaccination decisions, and they must be supported to provide trusted, credible information on vaccines." Communicating to parents and patients the value of vaccination and addressing their concerns without belittling them should be a skill of every healthcare worker – from midwives and nurses in rural health units, pediatricians in private clinics, to government officials who are the faces of public health in the media. In the age of fake news, countering misinformation is another necessary skill to provide parents with the correct information and empower them to make the right decision to vaccinate their children. There are prominent social media champions for vaccination, Dr. Edsel Salvana on Facebook and Dr. Peter Hotez on Twitter to name two, and they provide excellent examples on communicating about vaccines and vaccination – and as more doctors and other healthcare workers use social media to advocate for vaccination, equipping them with the right and effective social media communication tools becomes vital.

But how about healthcare workers' own vaccine confidence? Given their important frontline role in vaccination, what is the state of vaccine hesitancy among their ranks? There are data from developed countries showing that vaccine hesitancy is also present among HCWs; this needs to be measured and evaluated locally, too. When new vaccines are introduced, how should frontline workers be consulted by policymakers? What do HCWs know about side effects and how should pharmaceutical companies communicate this to them so they can communicate it to patients? How does the information, wrong or right, found in the internet and social media affect the vaccine confidence of HCWs? These questions need answers rooted in research and consultative measures to enable a robust vaccine trust among healthcare workers.

Studies show that people who trust doctors and nurses are likely to consider that vaccines are safe. Trust in the health system was also shown to translate to parents vaccinating their children. It is therefore important to enforce this trust with transparency and accountability. Addressing the concerns of transparency and accountability brought about by the Dengvaxia controversy can be a start to this. The licensing and procurement process of vaccines for the national immunization program should be above politics, and the DOH should be open to scrutiny of its processes. The Philippine constitution states that "Public office is a public trust," thus public officials both of, and outside, the Health Department should be aware of and accountable for the effect their words and actions have on public health. In addition to public officials, the Dengvaxia controversy demands a thorough introspection in the medical community on what lessons need to be learned. Trust in the health system has to be rebuilt by all stakeholders.

Lastly, vaccine trust must be regained by ensuring that the health system is functional - that when a mother, say, goes to a rural health unit as scheduled, there will be vaccines available there, otherwise, communication and trust-building will be for naught. The re-emergence of polio in the Philippines has added another challenge on an already over-burdened but under-resourced public service sector. Both resources and reform have to be at hand in the Department of Health. Human resource shortages, supply chain issues, and the challenges inherent in a decentralized system all need to be addressed. The creation of a National Immunization Technical Advisory Group (NITAG) should be legislated. Ad hoc responses to outbreaks should be replaced by policies that prioritize prevention, has a sustained communication effort, with an integrated role for research, and with an all-hands-on-deck approach that involves both public and private health delivery sectors.

The return of polio should prompt a response of "Never Again" from every Filipino. Restoring trust in vaccines and the vaccine program presents the first step in restoring the health of the public.

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Alvarado-Dela Cruz K, Pascual M & Luna-Dizon ME. The Clinical Profile and Outcome of Children with Dengue Encephalitis at the Philippine Children's Medical Center: A Retrospective Study from January 2011-June 2017

ORIGINAL ARTICLE

THE CLINICAL PROFILE AND OUTCOME OF CHILDREN WITH DENGUE ENCEPHALITIS AT THE PHILIPPINE CHILDREN'S MEDICAL CENTER: A RETROSPECTIVE STUDY FROM JANUARY 2011-JUNE 2017

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

ABSTRACT

BACKGROUND: Dengue, a mosquito-borne flavivirus, is hyperendemic in the Philippines. One of its rare complication is dengue encephalitis, characterized by altered sensorium, elevated liver enzymes, and high dengue-specific antibody titers. Previously known as non-neurotropic, dengue presents with an increasing incidence of neurologic manifestations.

OBJECTIVE: To describe the clinico-demographic profile and outcome of laboratory-confirmed dengue encephalitis patients.

METHODS: This is a retrospective study that used purposive sampling to describe laboratory-confirmed dengue encephalitis cases aged 0-18 years. The clinico-demographic profiles and outcomes were collected using chart review, and variables were analyzed using descriptive statistics.

RESULTS: 14 laboratory-confirmed cases were reviewed. Most (57%) were males aged 3 days-15 years. Fever lasted 3-11 days. Following nonspecific signs and symptoms, neurological manifestations developed within 1-5 days, the most common being seizures (71%). Majority (57%) had anemia. All, except one, exhibited leukopenia and thrombocytopenia. Elevated liver enzymes, bleeding parameter derangements, electrolyte, and glucose imbalances were noted. All were seropositive for dengue IgM, and 5 dengue IgM in the CSF. Most common EEG findings showed generalized slowing. Neuroimaging reports were normal in some or showed cerebral edema in the others. Half of the patients recovered fully, 3 showing partial recovery from neurologic changes, and 3 others had neurologic sequelae. One infant expired.

CONCLUSIONS AND RECOMMENDATIONS: Dengue encephalitis should be considered in patients living in an endemic country, presenting with fever with neurologic changes or elevated liver enzymes, with a risk for developing neurologic sequelae or death.

KEYWORDS: *Dengue Encephalitis, Neurotropic virus, Severe Dengue*

INTRODUCTION

Dengue is a major health problem in most tropical and subtropical areas[1] and is the most rapidly spreading mosquito-borne viral disease in the world. In the last 50 years, incidence has increased 30-fold with increasing geographic expansion to new countries and, in the present decade, from urban to rural settings. An estimated 50-million dengue infections occur annually and approximately 2.5 billion people live in dengue endemic countries.[2] The number of dengue cases reported annually to WHO has increased from 0.4 to 1.3 million in the decade 1996–2005, reaching 2.2 million in 2010 and 3.2 million in 2015.[6,7] In 2013 dengue was estimated to be responsible for approximately 3.2 million severe cases and 9000 deaths.[3] Severe dengue is a leading cause of serious illness and death among children in some Asian and Latin American countries.[3] Dengue encephalitis is an extremely rare manifestation of severe dengue disease.[12]

In the Philippines, in which dengue is hyperendemic; the incidence of dengue cases shows an increasing trend in recent years. In January 1 to December 31, 2018, the suspected dengue cases reported nationwide is 42% higher compared to the same time period in 2017, with case fatality rates increasing from 30% in 2015 to 55% in 2018.[37] The clinical spectrum of dengue fever ranges from asymptomatic infection to severe dengue and dengue shock syndrome. In 2009, WHO adjustments in the classification of the disease resulted in the recognition of two main presentations of dengue. These are referred to as dengue fever and severe dengue. Neurological dengue is classified as a form of severe dengue.[38,39]

Although dengue virus is classically considered non-neurotropic, in recent years, neurological manifestations of dengue have been documented.[12] Murthy has classified the spectrum of neurological manifestations seen in dengue into 3 categories: 1) those related to neurotropic effect of the virus, like: encephalitis, meningitis, myositis and myelitis; 2) those due to the systemic complications of infection, like: encephalopathy, stroke and hypokalemic paralysis, and 3) finally, post-infectious complications, like: encephalomyelitis, optic neuritis and Guillain Barré syndrome.[11] A prospective case-controlled study conducted by Cam et al. on 5,400 cases of dengue hemorrhagic fever (DHF) in Vietnam, has shown dengue infection causing encephalitis results to significant morbidity in terms of neurologic sequalae. Dengue-associated encephalopathy accounted for 0.5% of all cases. The mortality rate among children with dengue-associated encephalopathy was 22%.[14] Dengue encephalitis patients usually present with altered sensorium, elevated liver enzymes and high antibody titers at the time of admission.[10] Acute encephalitis, defined by the presence of an inflammatory process of the brain in association with clinical evidence of neurologic dysfunction, is a serious and potentially debilitating condition, which may lead to adverse outcomes of prolonged neurologic sequelae or death.

The incidence of dengue has grown dramatically around the world in recent decades. Neurologic involvement occurs in 4%-5% of confirmed dengue.[40] Dengue infection in patients with suspected central nervous system (CNS) infection is noted to range from 4.2% in southern Vietnam[28] to 13.5% in Jamaica[33] whereas, the incidence of dengue among patients with clinical manifestations of encephalitis-like illness ranges from 18%[41] to 22%.[33] Among confirmed neurological dengue cases studies have documented encephalitis to be the presenting clinical manifestation in 52%[33] to 56%.[28]

The annual incidence of dengue encephalitis is most likely underestimated, especially in developing countries because of problems with pathogen detection. In the Philippines, the Epidemiology Bureau of the Department of Health established the Philippine Integrated Disease Surveillance and Response (PIDSR) system in 2007, under which the surveillance on Acute Encephalitis Syndrome (AES) and Bacterial Meningitis (BM) falls.

An integrated surveillance for Acute Meningitis-Encephalitis Syndrome (AMES) was established in 2014 as a combination of both AES and BM, that collates data on both conditions. Presently, there are no local studies describing the clinico-demographic profiles and outcomes of dengue encephalitis cases in the Philippines.

This study aimed to provide clinico-demographic profiles and outcomes of pediatric cases of dengue encephalitis; to provide epidemiological data of such in the Philippines for better case detection, prognostication, prevention, counseling of patients and family members, public health interventions, work-up, and subsequent monitoring. Furthermore, the results of the study may be used as a baseline for further studies on dengue infection.

This study described the clinico-demographic profiles and outcomes of children with dengue encephalitis in a tertiary hospital in the Philippines from January 2011 to June 2017. Specifically, this determined the clinico-demographic features of children with dengue encephalitis in terms of the following: age, gender, geographic location, nutritional status, presenting features, clinical signs, history of previous dengue infection and subsequent outcome, receipt of dengue vaccine, presence of co-morbidities, laboratory examinations, and/or imaging techniques (complete blood count, ALT, AST, glucose, serum electrolytes, BUN, Creatinine, PT and PTT, Dengue NS1, Dengue IgG, IgM, CSF IgM-capture ELISA, EEG, Chest X-ray, Cranial ultrasound, Cranial CT scan and/or MRI).

Another objective was to determine the outcome of patients with dengue encephalitis in terms of: (a) Full Recovery (with complete resolution of neurologic signs and symptoms), (b) Partial Recovery (with partial resolution of neurologic signs and symptoms), (c) Presence of neurologic sequelae, or (d) Death.

METHODOLOGY

This is a retrospective observational study, that used purposive sampling to retrieve and review hospital charts of laboratory-confirmed dengue encephalitis cases aged 0-18 years.

Inclusion Criteria

All of the following criteria were fulfilled prior to study enrolment: (1) Children aged 0-18 years, (2) admitted at a tertiary hospital in the Philippines from January 2011 to June 2017, and (3) patients who fulfill the clinical case definition in AMES surveillance, and are laboratory confirmed cases of acute dengue encephalitis.

Exclusion Criteria

Patients with the following were excluded in the study: (1) bacterial, tuberculous, fungal, parasitic, other viral or immune etiology;(2) patients with encephalomyelitis (eg. Acute Disseminated Encephalomyelitis), or (3) patients without samples submitted for routine CSF and serum analyses.

The Child Neurology census from January 2011- June 2017 was reviewed, revealing 3,124 probable cases of Central Nervous System (CNS) infection, 209 cases of which having a final discharge diagnosis of encephalitis/ encephalopathy, records of which were retrieved for review. Of these, 18 cases were eventually discharged as dengue encephalitis/ encephalopathy.

The Acute Meningoencephalitis Syndrome (AMES) Surveillance reports from January 2011-June 2017 were retrieved from the National Reference Laboratory, to search for laboratory-confirmed cases of dengue encephalitis. Of the 18 cases discharged as dengue encephalitis/encephalopathy, 16 had dengue-specific IgM antibody in the CSF or serum sample detected by Dengue NS1 or IgM-capture ELISA. Also, four patients who were initially treated as cases of dengue encephalitis were excluded due to the presence of Japanese encephalitis-specific IgM (3 cases) and Chikungunya virus IgM (1 patient) in the CSF. A total of 14 cases were included in the study.

Definition of terms

An *Acute Meningoencephalitis Syndrome (AMES) Surveillance case* - is a person with sudden onset of fever and at least one of the following: change in mental status (including altered consciousness, confusion or inability to talk), new onset of seizures (excluding simple febrile seizures), neck stiffness and other meningeal signs.

Dengue encephalitis cases – are suspected dengue patients that meet the clinical case definition defined by AMES surveillance, and a laboratory confirmed dengue infection (as defined by the presence of dengue specific-IgM antibody in serum or CSF detected by dengue NS1 or IgM-capture ELISA, in the absence of co-infection with other etiologic agents).

Approval was obtained from the hospital's Institutional Review Board (IRB). Hospital charts of patients who fulfilled all of the inclusion, and none of the exclusion criteria were retrieved and reviewed.

The following clinico-demographic data were noted in the study-defined patient data sheet: age, gender, geographic location, nutritional status, clinical history, receipt of dengue vaccine, presenting features, clinical signs, duration of hospital stay, co-morbidities, management, as well as laboratory and imaging examinations done. Clinical outcomes were categorized as follows: full recovery, partial recovery from neurologic changes, presence of neurologic sequelae; or death. An attempt to retrieve and review the outpatient follow-up charts was done, of which none can be located. Neuroimaging and encephalogram results done post-hospital discharge were located, and were subsequently reviewed.

Descriptive statistics was used to summarize the clinical characteristics of the patients. Frequency and proportion were used for nominal variables, median and range for ordinal variables, and mean and standard deviation for interval/ratio variables. All valid data were included in the analysis. Missing variables was neither replaced nor estimated. STATA 12.0 was used for data analysis.

RESULTS

During the period covered by the study, 14 cases of laboratory-confirmed dengue encephalitis were recorded. All patients were referred to the intensive care unit. Of the 14 patients enrolled, 9 patients were managed as severe dengue, 4 as neonatal sepsis with CNS infection and 1 as Viral Encephalitis, unspecified. Eleven patients with one or a combination of the following concomitant illnesses: Pneumonia (7), Clinical sepsis (4), Generalized epilepsy with global developmental delay (1), Necrotizing fasciitis, chest (1), Patent Ductus Arteriosus (1) were identified, and were all subsequently managed during the hospital stay.

Table 1. Demographic and clinical profile of patients with dengue encephalitis (n=14)

	Frequency (%); Median (Range)
Age at onset (years)	2.5 years (3 days to 15 years)
Gender	
Male	8 (57.14)
Female	6 (42.86)
Region of Location/Residence	
NCR	10 (71.4)
III	2 (14.3)
IV - A	2 (14.3)
Weight (kg)	12.3 (2.1 to 65)
Height (cm) (n = 3)	61 (51 to 156.6)
BMI (kg/m^2) (n=3)	15.59 (15.38 to 21.23)
Nutritional assessment*	
Obese	2 (14.3)
Overweight	0
Normal	10 (71.4)
Wasted / underweight	1 (7.14)
Severely wasted	1 (7.14)
Day of illness upon admission	3 (1 to 6)
Duration of febrile phase (days)	6 (3 to 11)
Hospital stay (days)	13.5 (6 to 41)
Time of onset of fever to development of neurologic changes (days)	2 (1 to 5)
Presence of comorbidities/ concomitant illnesses	8 (57.14)
Previous hospitalization	1 (7.14)
Previous dengue infection	0
Intervention given**	
Intravenous fluid support	14 (100)
Antibiotics	10 (71.4)
Pressors	3 (21.43)
Rehabilitation	1 (7.14)
Received dengue vaccine	0

**Nutritional assessment is based on weight for age (z-score)[20], **Multiple response*

Clinical characteristics

All patients were admitted during the first week of illness, ranging from the 1st to the 6th day (median, 3rd day), presenting with fever, coupled

with nonspecific signs and symptoms (Table 2). There was gastrointestinal bleeding in two children, with hematemesis in one and coffee ground material in the orogastric tube in another. Three patients (21%) became jaundiced, with no evidence of hepatomegaly. Enlargement of the liver was noted in 2 patients (14%). (Table 2). The time that elapsed from the onset of the febrile period until the onset of the neurological changes ranged from 1 to 5 days (median of 2 days).

Table 2. Presenting symptoms and clinical signs of patients with dengue encephalitis (n=14)

Presenting symptoms	Frequency (%)
Fever	14 (100)
Decreased appetite/poor suck	11 (78.57)
Cough/colds	9 (64.3)
Vomiting	6 (42.9)
Irritability	5 (35.7)
Loose stools	4 (28.6)
Headache	3 (21.4)
Abdominal pain	2 (14.3)
Clinical Signs	
Rash	5 (35.7)
Flushed skin	4 (28.6)
Pallor	3 (21.4)
Jaundice	3 (21.4)
Bleeding	2 (14.3)
Abdominal enlargement	2 (14.3)
Hepatomegaly	2 (14.3)

Table 3 Neurologic findings in patients with dengue encephalitis (n=14)

Neurologic changes	Frequency (%)
Seizures Generalized Focal Both	10 (71.4) 7 (70) 1 (10) 2 (20)
Decreased sensorium/ Increased sleeping time	8 (57.14)
Behavioral changes	4 (28.6)
Disorientation	3 (21.4)
Incoherent words	2(14.3)
Aphasia	1 (7.1)
Neurologic examination findings	
Nuchal rigidity	3 (21.4)
Bulging anterior fontanel	2 (14.3)
Spasticity	1 (7.1)
Development of Babinski reflex	1 (7.1)
Hyporeflexia (DTR +1)	1 (7.1)

More than half (57%) of children developed decrease in sensorium. The youngest patient exhibited spasticity, nuchal rigidity, and a bulging anterior fontanel. Babinski reflex and hyporeflexia were noted in one 10-year-old patient. Seizures, mostly generalized (n=7), were recorded in 71% of patients, and were the most common reason for hospital admission. (Table 3)

Upon admission, more than half (57%) of children had depressed hemoglobin for age (Table 4), 5 (83%) of which were within normal range for weight based on nutritional assessment at the time of confinement. Only one (7.1%) patient, aged 6 years, developed hemoconcentration, an evidence of plasma leakage due to increased vascular permeability[19].

Among those tested, majority had elevated ALT (8 of 10) and AST (5 of 6). One patient with consistently normal BUN registered high creatinine levels (maximum of 114.92 µmol/L). Hypokalemia was noted in half the children whom serum electrolytes were measured, other results were mostly normal. Three had high glucose, while one had hypoglycemia. Partial prothrombin time was prolonged in 40% of 10 children, and PT INR in 50% of these. Half of the patients showed radiologic evidence of pneumonia, 3 (21%) showed pleural effusion.

Table 4. Laboratory results of patients with dengue encephalitis (n=14)

	Median ± SD (Range)	Frequency (%)		
		Normal	Decreased	
Hemoglobin (g/dL)	125.48 ± 17.45	6 (42.9)	8 (57.1)	
		Normal	Decreased	Hemo-concentrated
Hematocrit (%)	37.85 ± 5.48	6 (42.9)	7 (50)	1 (7.1)
		With leukopenia	No leukopenia	
WBC (1000 cells/mm^3)	9.23 ± 3.85 (1.7 to 28.4)	13 (92.9)	1 (7.1)	
		With thrombocytopenia	No thrombocytopenia	
Platelet count (cells/mm^3)	133.0 ± 77.0(4 to 400)	13 (92.9)	1 (7.1)	
		Normal	Elevated	
ALT (u/L) (n=10)	76.5 (13 to 3165)	2 (20)	8 (80)	
AST (u/L) (n=6)	190.5 (27 to 650)	1 (16.7)	5 (83.3)	
BUN (mmol/L) (n=4)	4.4 (1.05 to 5.1)	4 (100)	0	
Creatinine (umol/L) (n=5)	74 (27 to 91.46)	4 (80)	1 (20)	
		Normal	Decreased	
Serum sodium (mmol/L) (n=10)	140.57 ± 7.9	7 (70)	3 (30)	
Serum potassium (mmol/L) (n=10)	3.86 ± 0.4	7 (70)	3 (30)	
Serum calcium (mmol/L) (n=10)	2.22 ± 0.3	6 (60)	4 (40)	
		Normal	Elevated	
PT (INR) (n=10)	1.15 ± 0.2	5 (50)	5 (50)	
		Normal	Prolonged	
PTT (seconds) (n=10)	44.99 ± 10.5	5 (50)	5 (50)	
		Normal	Elevated	Decreased
Glucose (mg/dl)	88.31 ± 23.5	11 (78.6)	3 (21.4)	1(7.2)
		Normal	With Pneumonia	Pneumonia With Effusion
Chest Xray		7 (50)	7 (50)	3 (21.4)

All patients had CSF analysis done, 8 were collected during the first week of illness. Pleocytosis for age was seen in in only one patient. CSF white blood cells (WBC) ranges from 0-8 cells x 10^6/L (median 2.14 cells x 10^6/L), all with 100% lymphocytic predominance. Other findings included slight hypoglycorrhachia (14.3%), and a mild increase in the protein level (14.3%) in 2 patients (43 and 45% respectively). Majority of the patients (71.4%) had normal CSF analysis.

Table 5. CSF findings of patients with dengue encephalitis (n=14)

	Mean ± SD; Median (Range)	Frequency (%)	
		Colorless/ Clear	Xanthochromic/ Hazy
Gross exam		11 (78.6)	3 (21.4)
		Normal	With Pleocytosis
WBC (cells x 10^6/L)	2.14 ± 2.6	13 (92.9)	1 (7.1)
		Normal	Elevated
Protein (g/L)	0.33 (0.2 to 1.07)	12 (85.7)	2 (14.3)
		Normal	With Hypoglychorrachia
CSF: SERUM glucose	65.86 ± 17.8	12 (85.7)	2 (14.3)

Table 6. Dengue-specific test results of patients with dengue encephalitis (n=14)

	Frequency (%)	
	Positive	Negative
Dengue IgM (+) in CSF	5 (35.7)	9 (64.3)
Dengue IgM (+) in serum	14 (100)	0
Dengue IgG (+) in serum (n=6)	4 (66.7)	2 (33.3)
Dengue NS1 (+) in serum (n=2)	2(100)	0

Concomitant blood and CSF bacterial cultures were done on all patients, all of which were negative for any bacterial pathogen.

Table 7. Neuroimaging (Cranial CT scan/ultrasound) of patients with dengue encephalitis (n=9)

Frequency (%)						
Normal	Abnormal					
	6 (66.7)					
3 (33.3)	Cerebral edema			Meningeal enhancement	Thick, wavy echogenic sulci	Hyperechoic subdural and subarachnoid spaces
	5 (55.6)			2 (33.3)	1 (16.7)	1 (16.7)
	Diffuse	Tempro-parietal lobe	Capsulo - thalamic region			
	3 (60.0)	1 (20.0)	1 (20.0)			

Neuroimaging (Table 7) revealed intracranial changes in 67% of patients, with findings such as cerebral edema (55.6%), and meningeal enhancement (33.3%).

Abnormality in waveforms was seen in 7 (87.5%) of 8 children who underwent EEG. Findings included continuous slowing of the background activity (86%), focal slowing (71%) and epileptiform

discharges (29%). Follow up EEG done in three patients, 3 weeks to a month after hospital discharge showed normal results in 2 patients, and significant improvement in the generalized background slowing in one patient. The most commonly used medication for seizure control was phenobarbital (92.9%).

Table 8. Outcome of patients with dengue encephalitis

Outcome	Frequency (%)
Fully recovered from neurologic changes	7 (50)
Partially recovered from neurologic changes	3 (21.43)
Neurologic sequelae present	3 (21.43)
Death	1 (7.14)

DISCUSSION

Dengue virus belongs to the *Flaviviridae* family, which includes a number of neurotropic viruses such as Japanese encephalitis virus, St. Louis encephalitis virus, and tick-borne encephalitis virus.[14] The signs and symptoms, as well as the characteristic laboratory markers for severe dengue were not seen in the majority of our patients with dengue encephalitis. A study done by Mufazzar in 2006 supports this finding, as he found that not all patients with dengue encephalitis develop complications of severe dengue.[28]

Antenatal and post-partum dengue infection secondary to vertical transmission has been documented to occur in neonates in several earlier reports[23,24]. Interestingly, this study found four neonates who had dengue specific IgM via serology, three of which also had dengue IgM in the CSF. None of these neonates were suspected to have an acute dengue infection during the hospital admission and were instead treated as cases of neonatal sepsis. Review of the patients' clinical course revealed that all four neonates fulfilled the minimum criteria for probable dengue. CSF analysis was done due to the consideration of concomitant CNS infection, and samples were sent to AMES surveillance for analysis. Results of the AMES surveillance was not known during the hospital stay of the patients, and all four neonates were discharged. Three neonates fully recovered, while one still showed signs of fair suck, with improved activity upon discharge. Three out of four neonates demonstrated dengue IgM in the CSF, the exception also showing full recovery upon discharge. Two of the four neonates' mothers had an unremarkable maternal history. One mother was febrile upon delivery due to urinary tract infection, the mother of the neonate with partial recovery expired 5 days after delivery due to preeclampsia, and an unknown febrile illness. During the patients' hospital stay, there was no mention whether the mother was worked-up for the possibility of having acute dengue. It is yet to be established what the poor prognostic factors are for neonates presenting with dengue encephalitis, as there are limited studies regarding this.

Neurologic manifestations due to dengue have been well reported, and has previously been thought to result from the multisystem derangement that occurs in severe dengue infection, with liver failure, shock and coagulopathy causing cerebral insult as opposed to encephalitis defined by a localized invasion of the CNS. Recent studies, however[10,11,13,14,21], describe a possible direct neurotropic effect of dengue virus. The incidence of dengue with neurologic complications is unclear, with calculations ranging from 0.5%[14] to 6.2%[26] of DHF cases. Kankirawatana et al. states that 18% of children with suspected encephalitis in a Thai hospital were found to have dengue infection.[27] In the absence of a definitive histological examination of the brain, dengue encephalitis is exemplified by the identification of dengue specific antibodies or dengue antigen in the CSF. Detection of IgM in CSF is indicative of viral replication in CNS, but the titer is generally lower and short-lived when compared with serum, making it an unreliable marker. It is because of this that in previous studies, patients were considered as cases of dengue encephalitis when there is serologic evidence of dengue infection, coupled with focal neurologic manifestations or neuroimaging abnormalities. This

consideration has also been employed in this study. In previous studies, mechanism of CNS infiltration has been observed via (1) virus-induced, cytokine-mediated breakdown of the blood-brain barrier, (2) via infiltration of virus-infected macrophages, or (3) by direct invasion of the virus itself. In accordance with these recent reports, we found 5 (35.7%) of 14 patients had dengue-specific IgM in the CSF, indicating a localized infection of the CNS. These patients consisted of 3 neonates, and 2 children. Of the 3 neonates, 2 recovered completely prior to discharge, with hospital stay of 8 and 41 days respectively. One neonate with IgM positive CSF exhibited fair activity prior to discharge. Two other children with IgM positive CSF both stayed at the hospital for 27 days, one was discharged with minimal verbal output and occasional disorientation, and one exhibiting focal deficit and whom hypoxic-ischemic encephalopathy was also considered.

The clinical manifestations and findings in this study were consistent with those reported in the literature and reviews of dengue encephalitis. Fever was present in all cases. Following non-specific signs and symptoms, decreased sensorium and new onset seizures were the most common neurologic manifestations, the latter being the most common reason for consult and subsequent hospital admission. Elevation in liver enzymes, dengue-related nephropathy, glucose and electrolyte derangements, elevated prothrombin time, prolonged activated thromboplastin time, and signs of plasma leakage were seen in some of our patients. It has been well recognized that cerebral dysfunction may result from these findings, and may account for some neurologic manifestations seen. Interestingly, hemoconcentration was not observed in the cases seen in this study. The paucity of subjects limits the investigator in concluding a correlation exists between this observation and severe dengue in general. CSF analysis of the patients showed the following, a minority with slight hypoglycorrhachia and pleocytosis, all with absolute (100%) lymphocytosis, the findings of which were consistent with viral encephalitis in general. The most common EEG and neuroimaging findings were likewise consistent with dengue encephalitis.[10,11,13,14,21,27,35] Most patients manifested with generalized or focal background slowing via EEG, and neuroimaging findings ranged from being normal, to having evidence of cerebral edema, some with changes consistent with acute meningoencephalitis. Testing for correlation between established factors for poor prognosis, which were noted in some of the patients, such as extremes of age, under or over nutrition, presence of co-morbidities, signs of plasma leakage, hepatic involvement, and patient outcome could not be done due to the very limited subjects.

Among the *Flaviviridae*, antigenic cross-reactivity appears to involve a group-reactive antigen shared by all members. In patients with previous Japanese encephalitis, these circulating low-titer antibodies may show cross-reactivity with dengue virus. This was evident in the cases seen in this study as four patients who were initially treated as cases of dengue encephalitis, were excluded in this study due to the presence of Japanese encephalitis-specific IgM (3 cases) and Chikungunya virus IgM (1 patient) in the CSF.

On the basis of previous reports[10,11,13,14,21] and of the findings of this study, dengue infection encompasses an expanding clinical spectrum that rarely involves encephalitis due to a direct viral neurotropism.

Mortality due to dengue encephalitis varies from 5%[22] to 22%[14] in previous studies. The reported morbidity and mortality due to dengue encephalitis itself is low with most survivors recovering fully.[10,34,35] Documented sequelae from encephalitis included weakness, spasticity[35] and focal spasms.[36] Encephalitis accompanied by post-infectious neurological manifestations however may have a prolonged recovery. Our study limited our investigation to laboratory-confirmed dengue encephalitis in the absence of co-infection with other viruses in the CNS, and only a single mortality was observed. The single mortality observed in this

study is a 1-year-old male with dengue IgM antibody detected in the serum, who's immediate cause of death was dengue shock, presenting as generalized seizures and hypotension. Neurologic manifestations were observed in 6 (42.9%) of patients upon discharge, ranging from mild to severe. The presence of long-term or permanent neurologic sequelae cannot be inferred since the only follow-up data available were the follow-up EEG of two patients, which showed improvement in the generalized background slowing in one, and a normal EEG in another patient taken 3 weeks from discharge. It would be interesting to know the long-term outcome of each patient using an established outcome scoring system on subsequent patient follow-up consults, so as to determine whether neurologic changes that have been present on discharge would lead to eventual recovery or deterioration. This exercise, however, is beyond the scope of this study.

According to the World Health Organization (WHO), the real burden of dengue encephalitis is underreported. Although CSF analysis for dengue is locally available, and is government subsidized in sentinel hospitals under the national surveillance program, the relative contraindication of performing an invasive procedure in the context of a clinically unstable patient with thrombocytopenia, and the cost of the test in private institutions restricts definitive laboratory confirmation of dengue encephalitis. Clinical dengue infection in the presence of focal neurologic findings is suggestive of the disease, however, laboratory confirmation via CSF analysis is necessary to determine whether the encephalitis is due to dengue neurotropism, or a systemic consequence of severe disease itself.

Due to the potential risk for significant morbidity and mortality, it is recommended that dengue encephalitis be highly considered in patients with severe dengue so that prompt case detection and appropriate management ensue. The small sample size, heterogeneity of clinical profile, and patient response are probably responsible for outcome variations.

CONCLUSION AND RECOMMENDATIONS

In conclusion, dengue encephalitis is emerging as an important, albeit rare entity that should be entertained as a differential diagnosis in dengue patients with neurologic manifestations in all age groups. Likewise, it should be included in the differential diagnosis of any CNS infection in an endemic country, as evidenced by the 4 neonates managed as neonatal sepsis but turned out to be positive for dengue IgM.

It is recommended that prospective studies be done on this subject as we recognize the limitations of a retrospective study. Likewise, long-term follow-up on patients should be performed for prognostication.

REFERENCES

1. Liu JW, Khor BS, Lee CH, Lee IK, Chen RF, Yang KD. Dengue hemorrhagic fever in Taiwan. World Health Organization Dengue Bulletin. 2003; 27:3-24. 2.
2. Global Strategy for dengue prevention and control, 2012–2020. World Health Organization, Geneva, Switzerland, 2012. Accessed 10 Apr 2017 at http://apps.who.int/iris/bitstream/10665/75303/1/9789241504034_eng.pdf
3. Dengue and severe dengue (Fact sheet N°117). World Health Organization, Geneva, Switzerland, 2016 [cited 24 June 2016]. Available from: http://www.who.int/mediacentre/factsheets/fs117/en/
4. Republic of the Philippines Department of Health website. Accessed 15 Apr 2017.https://www.doh.gov.ph/sites/default/files/statistics/2016_Dengue_W47_1.pdf.
5. Tunkel AR, Glaser CA,Bloch KA, Sejvar JJ, Marra CM, Roos KL, Hartman BJ, Kaplan S, Scheld WM, Whitley RJ. The Management of Encephalitis: Clinical Practice Guidelines by the Infectious Diseases Society of America. CID Jun 2008:47.
6. World Health Organization (WHO) Regional Office for South-East Asia. Dengue: guidelines for diagnosis, treatment, prevention, and control. Special Programme for Research and Training in Tropical Diseases. 2009. Available from: 147. https://doi.org/WHO/HTM/NTD/DEN/2009.1
7. Global Strategy for dengue prevention and control, 2012–2020. World Health Organization, Geneva, Switzerland, 2012. Available from:

http://apps.who.int/iris/bitstream/10665/75303/1/9789241504034_eng.pdf

8. Cherry JD, Harrison GJ, Kaplan SL, Steinbach, MD, Hotez PJ. Feigin and Cherry's Textbook of Pediatric Infectious Diseases, 7th ed. 2014. Elsevier Saunders, USA. Ch. 45.
9. M. States,W. Advi, T. Grade, et al. Dengue vaccine: WHO position paper – July 2016. 29 JULY 2016, 91th YEAR. World Health Organization weekly epidemiological record; p.350
10. Rao SM, Pradeep M, Dnyaneshwar M and Alai T. Dengue encephalitis – clinical spectrum and outcome. Intern Med Inside. 2013; 1:8. http://dx.doi.org/10.7243/2052-6954-1-8
11. Murthy JM. Neurological complications of dengue infection. Neurol India 2010; 58: 581-584
12. Rao S, Kumar M, Ghosh S, Gadpayle AK. A rare case of dengue encephalitis. BMJ Case Rep 2013; doi:10.1136/bcr- 2012-008229. [4]
13. Deepak Madi et. al. Dengue Encephalitis – A Rare Manifestation of Dengue Fever.Asian Pacific Journal of Tropical Biomedicine 4, no. Suppl 1 (2014): S70-2 doi:10.12980/APJTB.4.2014C1006.
14. Cam BV, Fonsmark L, Hue NB, Phuong NT, Poulsen A, Heegaard ED. Prospective case-control study of encephalopathy in children with dengue hemorrhagic fever. Am J Trop Med Hyg 2001; 65(6):848-51. https://www.ncbi.nlm.nih.gov/pubmed/11791985 (accessed 19 April 2017).
15. Peacock JL, Peacock PJ. Research design. (ed). Oxford handbook of Medical Statistics. United States: Oxford University Press; 2011. pp. 60-61.
16. Department of Health National Epidemiology Center Public Health Surveillance and Information Division. Field Health Services Information System (2013) Manila, Philippines. Annual Report.
17. Philippine Integrated Disease Surveillance and Response Report. (2014) Department of Health. Manila, Philippines. Annual Report.
18. Committee on Immunization. Pediatric Infectious Disease Society of the Philippines. (May 20, 2016). Statement on the use of dengue vaccine. Manila, Philippines.
19. Technical working group. Philippine Pediatrics Society. (October 18, 2010) 2010 Interim guidelines on fluid management of dengue fever and dengue hemorrhagic fever. Manila, Philippines.
20. Philippine Pediatric Society. Preventive Pediatric Health Care Handbook, eighth ed., 2016.
21. Samanta M, Kundu, CK, Guha G, Chattergee S. Unique Neurologic manifestations of Dengue Virus in Pediatric Population: A Case Series. Journal of Tropical Pediatrics. 2012, Vol 58, No. 5.
22. Pancharoen C, Thisyakom U. Neurological manifestations in dengue patients. Southeast Asian J Trop Med Public Health 2001; 32:341-5.
23. Chin PS, Khoo PC, Hani, AW, Chem YK, Norizah I,Chua KB. Acute dengue in a neonate secondary to perinatal transmission. Med J Malaysia. 2008 Aug;63(3):265-6.
24. Chye JK, Lim CT, Ng KB, Lim JM, George R, Lam SK. Vertical transmission of dengue. Clin Infectious Diseases.1997
25. Porta M. A Dictionary of Epidemiology, 5th ed. NY. 2001. Oxford University Press; 5:p. 53.
26. Hendarto SK, Hadinegoro SR. Dengue encephalopathy. Acta Paediatr Jpn 1992;34:350-7.
27. Kankirawatana P, Chokephaibulkit K, Puthavathana P, Yoksan S, Somchai A, Pongthapisit V. Dengue infection presenting with central nervous system manifestation. J Child Neurol 2000;15;544-7.
28. Solomon T, Dung NM, Vaughn DW, Kneen R, Thao LT, Raengsakulrach B, et al. Neurological manifestations of dengue infection. Lancet 2000;355:1053-9.
29. Gulati S, Maheshwari A. Atypical manifestations of dengue. Trop Med Int Health 2007;12:1087-95.
30. Muzaffar J, Krishnan V, Gupta N, Kar P. Dengue encephalitis: why we need to identify this entity in a dengue-prone region. Sing Med J. Nov 2006. Vol.47: pp.975-7.
31. Administrative Order 2012-0006. Revised Dengue Clinical Case Management Guidelines 2011. Department of health of the Republic of the Philippines. 2012: 66-7.
32. Kliegman RM, Stanton BF, Geme GW III, Schor NF, De Maso DR, Denison MR, et al, editors. Nelson Textbook of Pediatrics. 20th ed. Philadelphia: Elsevier, Inc. 2016..
33. Jackson ST, Hann Chu JJ, Chia P, Morgan OS, Ng LC. Dengue encephalitis. Intech. 2011: 11-12. Available from: http://www.intechopen.com/books/flavivirus-encephalitis/dengue-encephalitis
34. Angibaud G, Luaute J, Laille M, Gaultier C. Brain involevement in dengue fever. J of clin neuroscience. Jan 2001, 8:63-5.
35. Pancharoen C, Thisyakorn U. Neurological manifestations in dengue patients. Southeast Asian J of Trop Med and Pub Health. Jun 2001, 32:341-5.
36. Soares C, Fairia L, Peralta LC, De Freitas MR, Pucchioni-Sohler M. Dengue infection: neulogical manifestations and cerebrospinal fluid analysis. J of Neurol sciences. Nov 2006, 249: 19-24.
37. Department of Health National Epidemiology Bureau, Public Health Surveillance and Information Division. Field Health Services Information System (2013-2018) Manila, Philippines. Annual Reports

38. WHO (1997) Dengue haemorrhagic fever: diagnosis, treatment, prevention and control. 2nd ed., Geneva: World Health Organization, 1997.
39. WHO (2009b) Dengue: Guidelines for diagnosis, treatment, prevention and control. World Health Organisation and Special Programme for Research and Training in Tropical Diseases, 2009.
40. Puccioni-Sohler, M., Soares, C. N., Papaiz-Alvarenga, R., Castro, M. J., Faria, L. C. & Peralta, J. M. (2009) Neurologic dengue manifestations associated with intrathecal specific immune response. Neurology 2009 Vol 27,(October 2009) pp.1413-7
41. Kankirawatana P, Chokephaibulkit K, Puthavathana P, Yoksan S, Apintanapong S, Pongthapisit V. (2000) Dengue infection presenting with central nervous system a manifestation. Journal of Child Neurology, Vol.15,(August 2000), pp.544-7

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Dagani G, Yu D, Camomot S & Lopez EK. The Antibiogram of Isolated Pathogens from Tracheal Aspirate among Intubated Patients 2 Months – 5 Years Old with Very Severe Pneumonia Admitted in Pediatric Intensive Care Unit of a Tertiary Hospital in Cebu City from January 2013 to December 2016

ORIGINAL ARTICLE

THE ANTIBIOGRAM OF ISOLATED PATHOGENS FROM TRACHEAL ASPIRATE AMONG INTUBATED PATIENTS 2 MONTHS – 5 YEARS OLD WITH VERY SEVERE COMMUNITY-ACQUIRED PNEUMONIA ADMITTED IN PEDIATRIC INTENSIVE CARE UNIT OF A TERTIARY HOSPITAL IN CEBU CITY FROM 2013-2016

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

ABSTRACT

Objective: To determine the antibiogram of tracheal aspirate cultures (TACS) among intubated children aged 2 months to 5 years old with very severe community-acquired pneumonia (CAP).

Methodology: A retrospective chart review using total enumerative sampling.

Results: 66 out of the 343 patients had positive TACS. The top 5 most common isolates were *Klebsiella pneumoniae* (37.8%), *Pseudomonas aeruginosa* (25.7%), *Acinetobacter baumanii* (15.1%), *Enterobacter cloacae* (12.1%) and Methicillin Resistant Staphylococcus aureus (MRSA) (6%). The gram-negative isolates were highly sensitive to amikacin and carbapenems. Majority of these patients (92.42%) had history of Pentavalent immunization. Majority of patients who were TACS positive had history of antibiotic use prior to admission (92.42%), mostly second-generation cepahalosporin (cefuroxime, 32.42%). High rates of resistance to ampicillin and gentamicin were noted for patients with *Klebsiella pneumoniae* and *Enterobacter cloacae* isolates. Majority of patients with *Klebsiella pneumoniae, Acinetobacter baumanii* and MRSA expired.

Conclusion/Recommendation: Majority of those patients with positive isolates had MDR organisms thus for patients with very severe CAP who already received antibiotic as outpatient, broad spectrum antibiotics should be considered as empiric therapy and TACS be done on all patients with very severe CAP.

KEYWORDS: *Pneumonia very severe, Multi-drug resistant organisms, Tracheal aspirate culture*

INTRODUCTION

Pneumonia is the leading cause of death in children worldwide.[1] Each year > 2 million children younger than 5 years die of pneumonia, representing approximately 20% of all deaths in children within this age group.[2]

In the developed world, the annual incidence of pneumonia is approximately 3-4 cases per 100 children less than 5 years old.[2] In North America the annual incidence in children younger than 5 years of age is 34-40 cases per 1000. European figures taken from a study conducted in Finland are similar at 36/1000/year >5 years.[4]

According to World Health Organization (WHO), although pneumonia can often be treated and cured, most child deaths occur in the world's poorest regions with highest incidence in Sub-Saharan Africa and South Asia.

The Philippines is one of the 15 countries that together account for 75% of childhood pneumonia cases worldwide. In children age <5 years, pneumonia is the leading cause of mortality, with a mortality rate of 23.4 per 100,000 population recorded in 2009.[8]

Many pathogens are responsible for Community Acquired Pneumonia (CAP) in children, most prominently viruses and bacteria. Investigators have used a variety of laboratory tests to establish a microbial etiology of CAP having different sensitivity, specificity and positive and negative predictive values that are dependent on the prevalence of the pathogen at the time of testing. Tracheal aspirate for gram stain and culture are recommended as an additional diagnostic test for pediatric patients with severe or life-threatening CAP.[2]

Determining the antibiogram of tracheal aspirate cultures among intubated patients classified as having very severe pneumonia is important to improve the clinical management of cases and guiding therapeutic decisions.[6,7] This study is significant because it will provide information on the common organisms isolated and its sensitivity pattern to different antimicrobials. Likewise, this study determined resistance rates of isolated respiratory pathogens to the most widely used antimicrobials in this institution.

The goal of this study was to determine the frequency distribution and sensitivity pattern of isolated pathogens from tracheal aspirate cultures among intubated patients aged 2 months to 5 years old with very severe community-acquired pneumonia admitted in the Pediatric Intensive Care Unit (PICU) from January 2013- December 2016.

Specifically, to determine through Tracheal Aspiration Culture and Sensitivity (TACS) the top 5 most common pathogens and their antimicrobial sensitivity and to determine the clinical profile of these patients as to:

- history of Hemophilus influenzae b (Hib) vaccination (a component of Pentavalent vaccine)
- outcome
- history of antibiotic use prior to admission

METHODOLOGY

A. Study Design

This was a retrospective study wherein medical charts of all intubated patients aged 2 months–5 years with very severe CAP admitted in the Pediatric Intensive Care Unit (PICU) of a Tertiary Hospital in Cebu City from January 2013-December 2016 were reviewed.

B. Study Population/ Sampling Technique

Purposive sampling employing total enumerative was done on all intubated patients aged 2 months – 5 years of age with very severe pneumonia who fulfilled following criteria:

INCLUSION CRITERIA

- All intubated patients aged 2 months – 5 years old with very severe CAP as a primary diagnosis and admitted direct to PICU
- Patients who are admitted and intubated not more than 3 days after admission so as to rule out possibility of a hospital-acquired pneumonia

EXCLUSION CRITERIA

- All intubated patients aged 2 months – 5 years old wherein PCAP is not the primary reason for intubation
- Those with co-morbidities i.e. cardiac anomalies, neurologic abnormalities
- Intubated patients admitted at the wards

C. Study Setting

The study was conducted at a Tertiary Hospital in Cebu City where retrieval and review of charts were done at the Medical Records Section and Microbiology Laboratory Department.

Review of the PICU census and Medical Records showed that the total intubated children aged 2 months to 5 years due to very severe CAP during the study period was 341. Out of these 341 patients, 243 (71.26%) patients had TACS taken less than 72 hours after admission only 66 patients (19.35%) had positive TACS results and were enrolled in study.

E. Data Analysis

The top 5 most common pathogens and their antimicrobial sensitivity were expressed thru descriptive statistics using percentage.

F. Ethical Consideration

An approval was obtained from the Technical and Ethical Review Board. Anonymity and confidentiality were maintained throughout the study period through assignment of coded numbers. The data and information gathered were kept by the primary author in a password protected file where only the primary investigator can gain access to. This study was self-funded and there was no conflict of interest from this study.

RESULTS

The total intubated children aged 2 months to 5 years due to very severe CAP during the study period was 341. Out of these 341 patients, 243 (71.26%) patients had TACS taken less than 72 hours and 66 patients (19.35%) had positive TACS results (see table 1). The most common isolated bacterial pathogen was *Klebsiella pneumoniae* followed by *Pseudomonas aeruginosa.*

Table 1. Distribution of the Tracheal Aspirate Pathogens (n= 66)

Tracheal Aspirate Growth	Pathogen	No.	%
1	*Klebsiella pneumoniae*	25	37.8%
2	*Pseudomonas aeruginosa*	17	25.7%
3	*Acinetobacter baumanii*	10	15.1%
4	*Enterobacter cloacae*	8	12.1%
5	*Methicillin Resistant Staphylococcus aureus (MRSA)*	4	6%
6	*Acinetobacter lwoffi*	1	1.5%
7	*Haemophilus influenzae*	1	1.5%

Antimicrobial Pattern

Klebsiella pneumoniae isolates were highly resistant to cefuroxime, ampicillin and ceftriaxone. Sensitivity to carbapenems and 4th generation cephalosporin was high while sensitivity to aminoglycoside was variable. Figure 1.

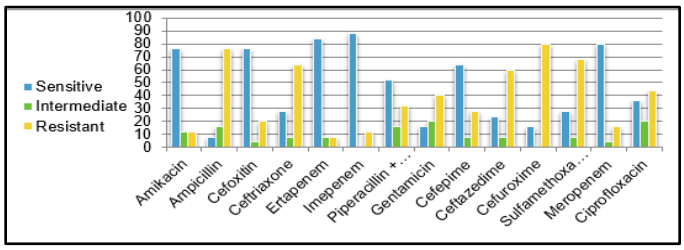

Figure 1. Percent Sensitivity and Resistance of *Klebsiella pneumoniae*

Pseudomonas aeruginosa were highly sensitive to ceftazidime at 94.1%, it also showed good sensitivity to piperacillin-tazobactam, 4th generation cephalosporin, ciprofloxacin, amikacin and carbapenems. Figure 2.

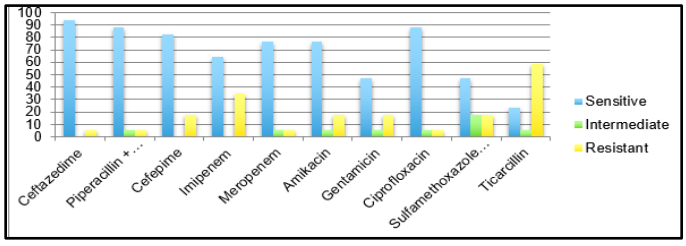

Figure 2. Percent Sensitivity and Resistance of *Pseudomonas aeruginosa*

Acinetobacter baumanii isolates were highly sensitive to amikacin and colistin. Other antimicrobials used for Acinetobacter such as carbapenems, cefepime, piperacillin-tazobactam had sensitivity rates ranging from 40-60%. This isolate showed high resistance rate to gentamicin, also an aminoglycoside. Figure 3.

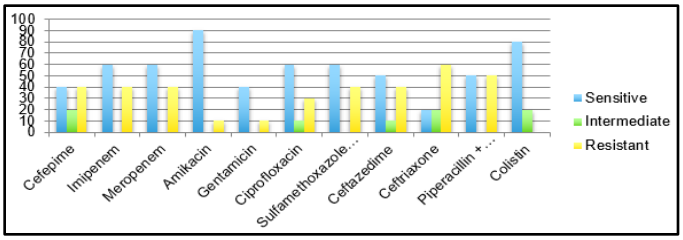

Figure 3. Percent Sensitivity and Resistance of *Acinetobacter baumanii*

Enterobacter cloacae were highly resistant to ampicillin, cefoxitin, cefuroxime and ceftriaxone. Carbapenems and aminoglycosides showed high coverage of this organism.

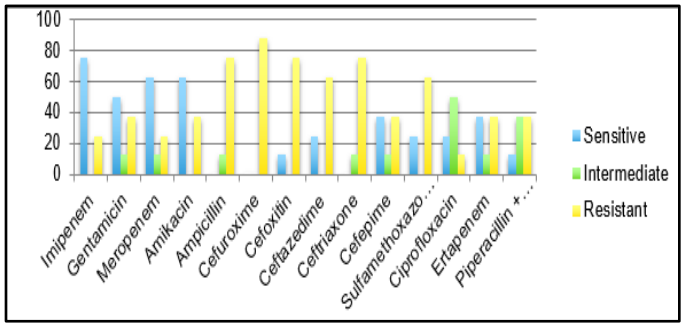

Figure 4. Percent Sensitivity and Resistance of *Enterobacter cloacae*

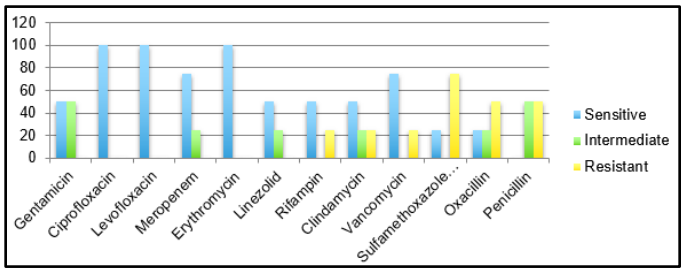

Figure 5. Percent Sensitivity and Resistance of MRSA

History of Immunization

Immunization is one of the factors that affect the etiology of a certain disease. Out of 66 patients with positive TACS, only 4 (6.06%) patients did not receive the Pentavalent vaccine as shown in figure 6. Of these 4 patients, 1 (6%) patient has positive TACS of *Haemophilus influenzae type b.*

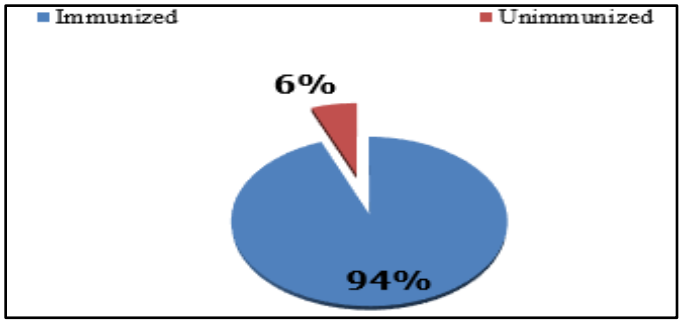

Figure 6. *Haemophilus influenzae b* (Hib) Immunization history of patients with positive TACS (n= 66)

Outcome

Infections caused by resistant microorganisms often fail to respond to the standard treatment, resulting in prolonged illness, higher health care expenditures, and a greater risk of death. As shown below, majority of patients with *Acinetobacter baumanii*, MRSA and *Klebsiella pneumoniae* died.

Table 2. Outcome of patients in relation to the isolated pathogens

Organism	Alive		Died	
	No.	%	No.	%
Acinetobacter baumanii (N= 10)	2	20%	8	80%
MRSA (N=4%)	1	25%	3	75%
Klebsiela pneumoniae (N= 25)	12	48%	13	52%
Pseudomonas aeruginosa (N=17)	9	53%	8	47%
Enterobacter cloacae (N = 8)	5	62%	3	38%

History of Antibiotic Use

Of the 66 patients with positive TACS, there were 61 (92.42%) patients who had previous history of antibiotic use prior to admission. Majority of the antibiotics given to the patients were cefuroxime, followed by amoxicillin and cefixime.

Table 3. History of Antibiotic used (n=61)

Name of antibiotics	Frequency
Cefuroxime	21 (34.42 %)
Amoxicillin	18 (29.50%)
Cefixime	7 (11.47%)
Clarithromycin	6 (9.83%)
Co amoxiclav	4 (6.55%)
Cefalexin	3 (4.91%)
Cefaclor	2 (3.27%)
TOTAL	61 (100%)

DISCUSSION

Acute respiratory infections namely pneumonia cause up to 5 million deaths annually among children less than 5 years old in developing nations. Of the estimated total of 12.9 million deaths globally in 1990 in children under 5 years of age, over 3.6 million were attributed to acute respiratory infections mostly due to pneumonia. This represents 28% of all deaths in young children and places pneumonia as the largest single cause of childhood mortality.[3] In the Philippines, more than 2 million children each year die due to pneumonia.[10] Pneumonia is defined by World Health Organization (WHO) as the presence of tachypnoea for which there is no apparent cause. Tachypnoea means respiratory rates above the following for age: at age 2-11 months, >50/min; age 1year–5 years >40/min; >5 years >20/min.[2,5] Severe pneumonia is defined as cough and tachypnoea plus one of the following:

chest indrawing, nasal flaring or grunting. Very severe pneumonia is defined as cough, tachypnoea plus one of the following: cyanosis, severe respiratory distress, inability to drink or vomiting everything, or lethargy/ unconsciousness/ convulsions. [2]

Etiologic agents of pneumonia vary depending on the age groups. Pneumonia can be due viruses, bacteria or fungi. Bacterial pathogens in newborns are Group B Streptococcus, *Escherichia coli, Klebsiella* species, and Enterobacteriaceae. For age 1-3 months, the most common pathogen is *Chlamydia trachomatis*. For preschool age, the following pathogens cause pneumonia: *Streptococcus pneumoniae, Haemophilus influenzae type b*, and *Staphylococcus aureus*. Less common pathogens for pre-schoolers are Group A Streptococcus, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*.[1] The identification of the common pathogens causing severe morbidity and mortality as well as their sensitivity patterns is of utmost importance in order to guide the physicians on proper antibiotic use.

Community Acquired–Lower Respiratory Tract Infections (CA-LRTIs) are becoming difficult to manage. These difficulties are related to the greatly increased emergence of resistance to the most widely used antibiotics against some of the bacterial pathogens involved in the development of the disease.[18]

This study gathered 66 (19.35%) positive TACS samples among 243 (71.26%). In this study, the top 5 most common pathogens isolates were mostly gram-negative organisms like *Klebsiella pneumoniae, Pseudomonas aeruginosa*, *Acinetobacter baumanii*, and *Enterobacter cloacae* and with one gram-positive organism namely the Methicillin Resistant *Staphylococcus aureus*. These findings were similar to those reported in 2016 ARSP wherein it stated that the top 3 most common pathogens isolated in respiratory specimens were *Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Acinetobacter baumanii.*[12] Similar pathogens were also reported in a study of Antibiotic Susceptibility Pattern in ICU at Philippine General Hospital, 2009 – 2013 and VSMMC Antimicrobial Susceptibility Pattern for both pediatric and adult patients, 2015.[24] These pathogens were also observed in mechanically ventilated children aged 0-59 months with Community Acquired Pneumonia admitted in PICU at Dhaka Hospital wherein forty-four of the 60 isolates were gram negative, in which 23% were *Klebsiella* species, 18% were *Escherichia coli*, 13 were *Acineto*bacter species and 4% were *Pseudomonas* species.[21] The pathogens isolated in this study are common hospital acquired pathogens and should rarely be found in these age groups. These results were not similar with various studies worldwide that showed *Streptococcus pneumoniae* to be the most common bacterial agent in children with pneumonia. Some possible explanation for this is that pneumococcal conjugate vaccine is part of the expanded program of immunization (EPI) vaccines being given in our local health center to this age group. Another is the widespread use of antibiotics that may have had an effect in the positivity of culture results especially for *Streptococcus pneumoniae* and lastly, it is important to note that majority of them didn't have any growth on TACS. Although included patients were those with tracheal aspirate done immediately after intubation, at most within 3 days and the duration time from admission was 72 hours, to exclude possibility of a hospital acquired infection or ventilator-associated pneumonia, most of the isolates were gram-negative organisms.

Antibiotic resistance is a worldwide problem, and unwise use of antibiotics has been recognized as a key contributor to the increasing rates of resistance. Antibiotic resistance refers specifically to the resistance to antibiotics that occurs in common bacteria that cause infections. Infections caused by resistant microorganisms often fail to respond to the standard treatment, resulting in prolonged illness, higher health care expenditures, and a greater risk of death.

A journal published on June 2003 in Malawi Medical Journal entitled Antibiotic Resistance Bacteria – An emerging Public Health Problem, stated the factors that favor the spread of antimicrobial resistance are as follows: general overuse of antibiotics, misuse of antibiotics by physician, misuse by unskilled practitioners and general public, poor quality antibiotics and increase in international travel[11]

In a study done in Dongguan, China from hospitalized children (0-5 years old) with Community Acquired Lower Respiratory Tract Infections (CA-LRTIs), the resistance rate of *Klebsiella pneumoniae* to ampicillin was 100% and co-trimoxazole at 75%.[18] Our results showed lower resistance level to ampicillin (76%), co- trimoxazole (68%) and gentamicin (40%). Cefuroxime showed the highest resistance rate at 80% in this study. This institution follows the WHO guidelines in treating pneumonia and the recommended treatment for pneumonia very severe according to WHO are ampicillin and gentamicin[14]. Based on the result of this study, there was a high resistance rate to ampicillin and gentamicin among the most commonly isolated pathogens in our institution. This result should be taken into account in updating the guideline on the treatment of very severe pneumonia in this institution. Although again it is important to note too that less than 20% of the patients had positive TACS isolate and majority didn't grow anything on TACS. Cefuroxime is one of the most widely prescribed antibiotics in the outpatient setting. This antimicrobial had high resistance rates to the commonly isolated pathogens. The threat of antimicrobial resistance is growing at an alarming rate and the situation is perhaps aggravated in developing countries due to gross abuse in the use of antimicrobials. It is well known that any use of antimicrobials however appropriate and justified, contributes to the development of resistance, but widespread unnecessary and excessive use makes the situation worse.[15] A study done by Cheol-In Kang et al, found that the recent use of cephalosporins appeared to be a risk factor for extended-spectrum cephalosporin (ESC) resistance in *K. pneumoniae* bacteremia.[17]

The emergence of carbapenem-resistant *Pseudomonas aeruginosa* has been an increasing problem in many parts of the world.[18] The use of prior antibiotic treatment was recognized as the only risk factor associated with CAP caused by multidrug resistant *P. aeruginosa*.[20] The resistance level of *P. aeruginosa* to imipenem is 35.2% but lower in meropenem (5.8%) in this study. Ceftazidime which has a good anti-Pseudomonal activity has a low resistance rate at 5.8% which was much lower compared to the result done in Dongguan, China wherein the resistance of *Pseudomonas aeruginosa* to ceftazidime was 13.61 and 30.99% in a separate study done in children 1-10 years old with lower respiratory tract infection in Nepal.[19]

Acinetobacter baumanii have become resistant to many classes of antibiotics.[10,16] In this study we noted that there was already an increasing rate of carbapenem resistance at forty percent and this reduces the existing therapeutic option. However, colistin as one of the choices in treating the Multidrug-resistant *Acinetobacter baumanii*, have the highest sensitivity rate of 90%. Although in this Institution, colistin is seldom used due to unavailability of this medication.

Community Acquired Lower Respiratory Tract Infections caused by *Enterobacter cloacae* has become a major worldwide problem. In a study done in patients under 5 years old with Community acquired Pneumonia admitted in Yulin Hospital, China, of the 759 samples tested, 177 strains were gram negative bacteria. The positive detection rate for *Enterobacter cloacae* was 8.45% and the isolates were completely resistant to amoxicillin and cefazolin at 100%, were resistant to ampicillin up to 96%, but had 100% sensitivity rate to levofloxacin. In our study, the highest resistance rate was to cefuroxime at 87.5% and ampicillin, ceftriaxone and

cefoxitin at 75%. This is alarming as these drugs are the first-line antibiotics we use for CAP. This resistance may be due to the production of constitutive AmpC B-lactamase enzyme by *E. cloacae* that exhibits a high frequency of enzymatic resistance to broad-spectrum cephalosporins.[22]

MRSA isolates were quite few but noteworthy is that out of the 4 patients with MRSA isolate, 3 of them expired and worrisome is the resistance rates noted to clindamycin and vancomycin, the drugs being given to MRSA.

While antibiotics are used for treatment, Immunization is the primary mode of prevention of infectious diseases. Prior immunization may reduce severity of disease, provide protection against shedding of pathogens and even raise the threshold load of pathogens required for infection.[15] In this study, out of 66 patients with positive TACS, only 4 (6.06%) patients did not receive the Pentavalent vaccine, wherein *Haemophilus influenzae type b* is included. Of these 4 patients, 1 patient has positive TACS to *Haemophilus influenzae type b*. Through this, we can appreciate the protective impact of immunizations received by the patients. Despite availability of vaccines, we still don't get 100% immunization rate in the intended population. [15]

Infection due to *Streptococcus pneumoniae* is a leading cause of morbidity and mortality in younger children, especially in developing countries. In this study, due to the limitation of a retrospective chart review the history of pneumococcal vaccination was not included as most of the charts didn't provide this information. It would have been an important finding if indeed we were not able to isolate any Streptococcus pneumoniae because of high immunization coverage for PCV.

Majority of patients with *Klebsiella pneumoniae, Acinetobacter baumanii* and MRSA expired with the following rate 52%, 80%, 75% respectively. The very high mortality rates is alarming considering that these patients come in with community-acquired pneumonia. *Acinetobacter baumanii* is recognized to be among the most difficult antimicrobial-resistant gram-negative bacilli to treat. This organism tends to occur in immunosuppressed patients and has the ability to survive under a wide range of environmental conditions and thus greatly limits the therapeutic options for patients who are infected with this organism.[10] A study done by Wah-Shing et al entitled Fulminant Community Acquired *Acinetobacter baumanii* Pneumonia as a Distinct Clinical Syndrome, the Community Acquired Pneumonia *A. baumanii* appears to be a unique clinical entity with a high incidence of bacteremia, ARDS, DIC and death when compared to Hospital Acquired Pneumonia *A. baumanii*.[16]

The results of this study highlight the varying levels of drug resistance amongst pathogens isolated in children with very severe pneumonia, and the need to control the increasing resistant strains before it reaches the alarming levels in this region. Of those with positive TACS and supposedly having CAP, the organisms isolated were more of the gram-negative organisms commonly seen in hospitalized patients. Rational antibiotic use in and out of the hospital cannot be overemphasized.

RECOMMENDATIONS

This study is limited by its retrospective and descriptive design. Thus, it is recommended that a prospective experimental study be conducted to collect a more robust data on various risk factors like previous antibiotic administration, immunosuppression, malnutrition, exposure to smoking etc that might affect the bacterial etiology of CAP and control for variables like receipt of vaccination.

For patients with very severe CAP who already received antibiotic as outpatient, the clinician should consider starting broader spectrum antibiotics and ensure that TACS be done as the possibility of having a MDR organism is there. The presence of an organism in gram staining, the result of which is obtained earlier than TACS can alert a physician to possibly start a broader spectrum

antibiotic since those with isolates mostly had MDR organisms. Prompt institution or shifting to an appropriate antibiotic is likewise recommended once results of TACS are available.

The researcher recommends strengthening the Antibiotic Stewardship in this institution if possible, to include the OPD in the hope of decreasing the incidence of multidrug resistant organisms.

The result of this study can be taken into consideration in the revision of the treatment protocols in very severe cases of pneumonia admitted in PICU of this hospital.

REFERENCES

1. Center for disease control and prevention. Pneumonia. [Online]. Available from: https://www.cdc.gov/pneumonia/index.html. [Accessed December 2017]
2. Bennett, et al, N.J. What is included in the PIDS and the IDSA guidelines for the management of community-acquired pneumonia (CAP) in infants and children older than 3 months?. [Online]. Available from:https://www.medscape.com/answers/967822-23630/what-is-included-in-the-pids-and-the-idsa-guidelines-for-the-management-of-community-acquired-pneumonia-cap-in-infants-and-children-older-than-3-months [Accessed January 2019]
3. Lakhanpaul, M, Atkinson, M, Stephenson, T. Community acquired pneumonia in children: a clinical update. BMJ Journal. 2004;89(2): 29-34
4 Harris, Michael & Clark, Julia & Coote, Nicky & Fletcher, Penny & Harnden, Anthony & McKean, Michael & Thomson, Anne. (2011). British Thoracic Society guidelines for the management of community acquired pneumonia in children: Update 2011. Thorax. 66 Suppl 2. ii1-23. 10.1136/thoraxjnl-2011-200598.
5. Philippine Academy of Pediatric Pulmonologists, Inc. PAPP PERSPECTIVE 3rd PAPP Update [2016] in the Evaluation and Management of Pediatric Community-acquired Pneumonia 2016 PAPP Task Force on pCAP. (3rd ed.). Philippines: 2016.
6. Philippine Academy of Pediatric Pulmonologists, Inc. Update in the Evaluation and Management of Pediatric Community-acquired Pneumonia 2008 PAPP Task Force on pCAP. (1st ed.). Philippines: 2008.
7 World health organization. Focus on Pneumonia. [Online]. Available from: http://www.wpro.who.int/philippines/typhoon_haiyan/media/Pneumonia.pdf?ua%20=%201 [Accessed 30 November 2017]
8 Pneumonia: Tops Causes Of Death Among Pinoy Children Retrieved From: http://www.interaksyon.com/article/24063/pneumonia-tops-causes-of-death-among- pinoy-children [Accessed 24 September 2015]
9 Perez , F, Hujer, A.&.K, Decker, B, Rather, P, Bonomo, R. The Global Challenge of Multidrug Resistant (MDR) Acinetobacter baumannii. Antimicrobial agents and chemotherapy. 2007;51(10): 3471-3484
10 Komolafe OO. Antibiotic resistance in bacteria - an emerging public health problem. *Malawi Med J*. 2003 Jun;15(2):63-7. doi: 10.4314/mmj.v15i2.10780. PMID: 27528961; PMCID: PMC3345436.
11 Antimicrobial Resistance Surveillance Reference Laboratory. Antimicrobial Resistance Surveillance Program in Philippines. 2016 Data Summary Report.pp.2,22
12 Garcia, E, Makalinaw , S, Manipon, M.L.B. . Prevalence Of Healthcare-Associated Infections Among The Pediatric Patients Admitted At Philippine General Hospital From The Years 2011-2014. Pediatric Infectious Diseases Society of the Philippines Journal. 2015;16(1): 12-20.
13 World Health Organization. Hospital Care For Children. Guidelines for the Management of Common Childhood Illnesses, 2nd edition.p80-90
14 Ayukekbong, J, Ntemgwa, M, Atabe, A. The Threat of Antimicrobial Resistance in Developing Countries: Causes and Control Strategies. Antimicrobial Resistance Infection Control. 2017;6(47)
15 Leung, W.S, Chu, C.M, Tsang, K.Y, Lo, F.H.&.K.F, Ho, P.L. Fulminant Community-Acquired Acinetobacter baumannii Pneumonia as a Distinct Clinical Syndrome. Antimicrobial Resistance Infection Control. 2017;129(1): 2006
16 Kang CI, Kim SH, Bang JW, Kim HB, Kim NJ, Kim EC, Oh MD, Choe KW. Community-acquired versus nosocomial Klebsiella pneumoniae bacteremia: clinical features, treatment outcomes, and clinical implication of antimicrobial resistance. *J Korean Med Sci*. 2006 Oct;21(5
17 He et al. Antimicrobial Resistance in Bacterial Pathogens among hospitalized Children with Community Acquired Lower respiratory Tract Infections in Dongguan, China (2011- 2016).BMC Infectious Diseases (2017)17:614

18 Salman Khan et.al., Bacteria Etiologic Agents causing Lower Respiratory Tract Infections and their Resistance Patterns. Iran Biomed J. 2015;19(4):240-246

19 Martin-loeches, C, Garcia-Vidal, C, San Jose, A, Torres, A. Microbial Etiology of Pneumonia: Epidemiology, Diagnosis and Resistance Patterns. Int J Mol Sci. 2016;17(12)

20 Shahunja K.M. et al. Bacterial Isolates from Tracheal Aspirates and their Anti- Microbial Susceptibility in Mechanical –Ventilates Children with Pneumonia Admitted to an Urban Critical Care Ward. Bangladesh Crit Care J September 2014; 2 (2): 60-64

21 Davin-Regli A, Pagès JM. Enterobacter aerogenes and Enterobacter cloacae; versatile bacterial pathogens confronting antibiotic treatment. *Front Microbiol*. 2015 May 18;6:392. doi: 10.3389/fmicb.2015.00392. PMID: 26042091; PMCID: PMC4435039.

22 Mohammod JC, Tebruegge M, La Vincente S, Graham S, Duke T.Pneumonia in Severely Malnourished Children in Developing Countries – Mortality risk, Etiology and Validity of World Health Organization Clinical Signs: A Systematic Review. Tropical Medicine and International Health (2009) 14(10):1173-1189

23 Vicente Sotto Memorial Medical Center. Antimicrobial Susceptibility Pattern. VSMMC ICC; 2015

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Calderon A & Garcia RD. Childhood Meningitis in an Urban Tertiary Medical Center: A 20-year Review

ORIGINAL ARTICLE

CHILDHOOD MENINGITIS IN AN URBAN TERTIARY MEDICAL CENTER: A 20-YEAR REVIEW

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

ABSTRACT

Background: Meningitis is a neurological emergency causing significant morbidity and mortality. This research determined the etiologies, clinical presentation, and ancillary work-up findings of different types of meningitis.

Objective: To characterize the documented pediatric meningitis cases in a tertiary hospital admitted between January 1, 1997 to August 31, 2017.

Methods: This was a retrospective study which entailed review of charts of all pediatric cases 0 to 18 years old with a discharge diagnosis of meningitis (bacterial, viral, tuberculous or fungal) from January 1, 1997 to August 31, 2017 at an urban tertiary medical center.

Results: This study included 127 subjects, where 74 (58.3%) had bacterial, 34 (26.8%) had viral, 17 (13.4%) had tuberculous, and 2 (1.6%) had fungal meningitis. *Streptococcus pneumoniae* (12.2%), *Haemophilus influenzae* type b (6.8%) and *Salmonella enteritidis* (6.8%) were the top bacteria identified. Neonatal infections were caused by gram-negative bacilli (66.7%) and gram-positive cocci (33.3%). Bacterial, tuberculous, and viral meningitis were seen in the 1-11 months, 2-4 years and 5-10-year age groups respectively. Prolonged fever (mean 27.2, median 14 days) and cranial nerve palsies (23.5%) were noted in tuberculous meningitis (TBM). The highest CSF mean WBC (2043±9056 WBC/μL) and mean protein (300±365.6mg/dL) were seen in bacterial and tuberculous meningitis respectively. The combination of hydrocephalus, basal enhancement and infarct was unique to patients with tuberculous meningitis. Recurrent seizures were the most common complication of bacterial (36.5%), viral (20.6%) and tuberculous (100%) meningitis. Ceftriaxone (24.3%), acyclovir (38.2%), and isoniazid/rifampicin/pyrazinamide/ethambutol (76.5%) were the most common antimicrobials for bacterial, viral, and tuberculous meningitis. Fever duration before admission was significantly longer in TBM (14 days) than in viral (4 days) and bacterial meningitis (2 days). Length of hospital stay for viral meningitis (6.5 days) was significantly shorter than for TB (14 days) and bacterial meningitis (12 days). Mortality rates were 12% and 11% for bacterial and viral meningitis respectively. No mortality was seen in patients with TB and fungal meningitis.

Conclusions: In this 20-year review of childhood meningitis, bacterial meningitis was the most common type of pediatric meningitis which presented with marked CSF pleoctyosis. The longest fever duration and the highest proportion of cranial nerve involvement were seen in TBM, which also had the unique combined findings of leptomeningeal enhancement, hydrocephalus and infarct on imaging. Ceftriaxone was the most commonly used antibiotic for bacterial meningitis, except in neonates where a combination of cefuroxime-amikacin was initially given until microbiological confirmation became available. Recurrent seizures were the most common complication of bacterial, viral and TB meningitis. The shortest hospital stay with the highest full recovery rate was seen in viral meningitis.

KEYWORDS: *meningitis, clinical manifestations, ancillary findings, treatment, outcomes*

INTRODUCTION

Meningitis is a life-threatening disease, and despite the availability of vaccines, effective antimicrobials and advances in critical care, it still belongs to the Department of Health's (DOH) top 10 causes of childhood mortality[1]. Based on the Philippine Pediatric Society (PPS) registry, meningitis of different etiologies accounts for only a small percentage of all reported illnesses (0.72%) in the past ten years. However, these infections have a significant mortality rate (9 to 19%)[2]. Meningitis is caused by different pathogens that produce similar symptomatology. This underscores the importance of seeking microbiological confirmation for definitive management. The high risk for significant pediatric morbidity and mortality that this disease confers calls for prompt management pending microbiologic confirmation.

The etiologies of meningitis are age- and setting-specific and may vary over time as a function of local vaccination policies and practices hence, epidemiologic data are indispensable. Locally, the most common bacterial pathogens in the different pediatric age groups are: gram negative enteric bacilli for neonates and infants up to 2 months of age and Hemophilus *influenzae type b* and *Streptococcus pneumoniae* for infants and children 3 months to less than 5 years old. *Neisseria meningitidis* may occur sporadically or in epidemics, with 80-90% of cases presenting as meningitis[3]. *Mycoplasma pneumoniae*, a common cause of respiratory tract infection in children 5 years and up, can also cause central nervous system complications. Meningitis and meningoencephalitis are its most common extra- pulmonary complications, affecting about 2.6 to 7% of patients with *Mycoplasma pneumoniae* infection[4]. Enteroviruses (i.e., coxsackievirus B, echoviruses) are the leading causes of viral meningitis in children, after the advent of mumps, measles, and rubella (MMR) vaccination. In addition, non-polio human enteroviruses are also a leading cause of aseptic meningitis (80-92%). Other common causes are herpes simplex virus (HSV) and varicella zoster virus (VZV)[5,6]. Tuberculous meningitis (TBM) is the most severe form of tuberculosis (TB). It is associated with a 16% mortality and 33% risk of intermediate or severe disability among survivors at the end of treatment, with the highest risk seen among infants and children under 2 years of age[7]. The likelihood of TBM increases in the presence of a sub-acute course, involvement of cranial nerves, and basal enhancement on CT scan[8,9,10]. Fungal meningitis is relatively rare. The most common cause of fungal meningitis is *Cryptococcus neoformans*, with an incidence of 0.016-100 cases/100,000 children. It should be considered in any child with fever, prolonged headache, vomiting and focal neurologic signs[11,12,13,14]. When used in conjunction with clinical and laboratory findings, epidemiologic data can guide the clinician in the diagnosis and in the choice of empiric antimicrobials.

In a resource-deficient country like the Philippines, reducing morbidity and mortality relies heavily on reliable local data on the clinical profile and epidemiology of CNS infections. Identification of age- and setting-specific etiologic agents is important to help the clinician in empiric treatment before results of diagnostic work-ups become available. This study was undertaken to characterize the documented pediatric meningitis cases in a tertiary hospital admitted between January 1, 1997 to August 31, 2017. Specifically, this study was done to (1.) determine the distribution of cases according to major etiologies of meningitis (bacterial, viral, tuberculous and fungal); (2.) to describe the age distribution, age distribution, clinical manifestations, ancillary work-up results, length of admission, treatment, complications and outcomes for each major etiologies; and (3.) to compare them as to their range and median duration of fever, range and median length of hospital stay and proportion of various outcomes.

METHODOLOGY

Study Design and Setting

This was a retrospective study where records of patients admitted between January 1, 1997 to August 31, 2017 with a discharge diagnosis of meningitis (bacterial, viral, tuberculous or fungal meningitis) were identified and reviewed.

Method

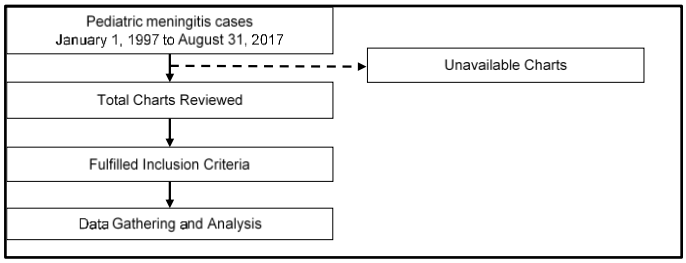

Figure 1. Flow of Study Participants

Inclusion Criteria

All admitted pediatric patients who had a final diagnosis of meningitis (bacterial, viral, tuberculous or fungal) were included in the study.

Exclusion Criterion

Patients diagnosed with meningitis, but who did not undergo CSF analysis, were excluded.

Data Gathering

Demographic, clinical, and microbiological information for each patient were collected from the medical records. The patient list was obtained from the ArchiveOne database, census of floors and ICU admissions from previous years, and records of infectious disease specialists and neurologists. Data collection lasted for two months.

Data Processing

Data encoding was done using Microsoft Excel, and completeness, consistency, and errors among the answers were checked.

Statistical Analysis

Data analysis was performed using STATA version 15. Mean and standard deviation were used to present quantitative data. Frequency distributions were used for categorical data. Kruskal-Wallis Test was used to compare quantitative data by etiology, followed by Dunn's test as post-hoc test. Chi-square Test or Fischer's Exact Test, whichever was applicable, was used to compare categorical data. All p-values less than 0.05 were considered statistically significant.

Ethical Considerations

The study was conducted according to the ethical principles based on the Declaration of Helsinki, WHO guidelines, and International Harmonization—Good Clinical Practice, and National Ethics Guidelines for Health Research. The research protocol underwent approval by the Institutional Review Board (IRB).

RESULTS

Demographic Data

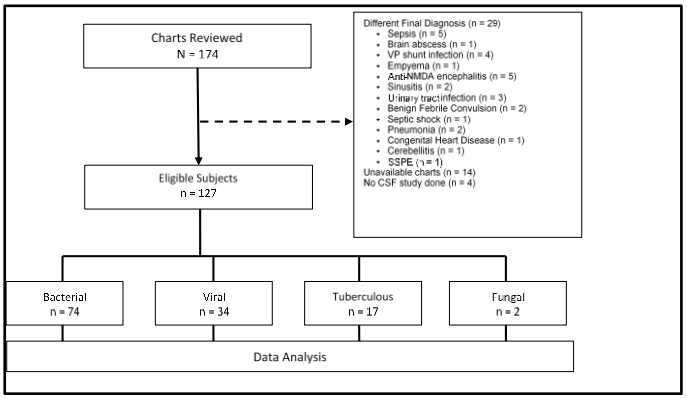

Figure 2. Methodology Flowchart

A total of 174 cases were identified based on the data gathering process stated earlier, but only 127 were included in the data analysis (see figure 2). Forty-seven cases were excluded, of which 29 did not have meningitis

as a final diagnosis upon rechecking of charts, 4 had no CSF studies, and 14 were unavailable.

Of the 127 patients, 74 (58.3%) had bacterial, 34 (26.8%) had viral, 17 (13.4%) had tuberculous and 2 (1.6%) had fungal meningitis. A male predilection was demonstrated for all except fungal meningitis.

Incidence peaked at two age groups: 1-11 months (25.2%) and 5-10 years old (23.6%). The most common age group for the different types of meningitis were: 1-11 months old for bacterial meningitis, 2-4 years old for TBM, and 5-10 years old for viral meningitis.

Bacterial Meningitis

Table 1. Specific Etiologic Agents and Age Group Distribution for Bacterial Meningitis, January 1, 1997 to August 31, 2017 (n=74)

Etiologic agent	0-7 days No.(%)	8-30 days No.(%)	1-11 months No.(%)	12-23 months No.(%)	2-4 years No.(%)	5-10 years No. (%)	11-15 years No.(%)	16-18 years No.(%)	Total (%)
th Organisms Isolated									**41 (55.4)**
Gram Positive									**18 (24.3)**
Streptococcus pneumoniae	0(0.0)	0(0.0)	4 (5.4)	1 (1.4)	2(2.7)	2(2.7)	0(0.0)	0(0.0)	9(12.2)
CONS (Staphylococcus epidermidis, capitis, staphylococcus hemolyticus)	0(0.0)	1 (1.4)	3(4.1)	0(0.0)	0(0.0)	0(0.0)	1(1.4)	0(0.0)	5(6.8)
Streptococcus agalactiae (GBS)	0 (0.0)	2(2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0(0.0)	0 (0.0)	0 (0.0)	2(2.7)
Micrococcus spp.	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0(0.0)	1 (1.4)	0 (0.0)	1(1.4)
Oxacillin-Resistant Staphylococcus aureus(ORSA)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0(0.0)	0 (0.0)	0 (0.0)	1(1.4)
Gram Negative									**23 (31.1)**
Hemophilus influenzae B	0 (0.0)	0 (0.0)	4 (5.4)	1 (1.4)	0 (0.0)	0(0.0)	0 (0.0)	0 (0.0)	5(6.8)
Salmonella enteritidis	0 (0.0)	1 (1.4)	3 (4.1)	0 (0.0)	0 (0.0)	0(0.0)	0 (0.0)	0 (0.0)	4(5.4)
Neisseria meningitides	0 (0.0)	1 (1.4)	2 (2.7)	0 (0.0)	0 (0.0)	0(0.0)	0 (0.0)	0 (0.0)	3(4.1)
Elizabethkingia meningoseptica/ Flavibacterium Meningosepticum/ Chryseomonas meningospetica	2 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0(0.0)	0 (0.0)	0 (0.0)	3(4.1)
Acinetobacterspp	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0(0.0)	0 (0.0)	0 (0.0)	1(1.4)
Pseudomonas aeruginosa	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0(0.0)	0 (0.0)	0 (0.0)	1(1.4)
E. coli	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0(0.0)	0 (0.0)	0 (0.0)	1(1.4)
Klebsiella pneumonia	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0(0.0)	0 (0.0)	0 (0.0)	1(1.4)
Burkholderia cepacia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0(0.0)	1 (1.4)	0 (0.0)	1(1.4)
Proteus mirabilis	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0(0.0)	0 (0.0)	0 (0.0)	1(1.4)
Serratia marcenscens	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0(0.0)	0 (0.0)	0 (0.0)	1(1.4)
Enterobacter cloacae	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0(0.0)	0 (0.0)	0 (0.0)	1(1.4)
organism isolated	0 (0.0)	3 (4.1)	7 (9.5)	0 (0.0)	5 (6.8)	13(17.6)	4 (5.4)	1 (1.4)	**33(44.6)**

In bacterial meningitis, 55.4% of cases had organisms identified either by culture (CSF and/or blood), by latex agglutination or by CSF Gram's staining. Among these laboratory-confirmed cases, 31.1% were due to gram-negative organisms. Overall, the most commonly-isolated organism was *Streptococcus pneumoniae* (12.2%). The other commonly identified organisms were *Haemophilus influenzae* type b (Hib) (6.8%), coagulase-negative staphylococci (CONS) (6.8%) and *Salmonella enteritidis* (5.4%). See table 1.

Streptococcus pneumoniae was seen in children 1 month to 10 years old. All cases of Hib meningitis were in children younger than 2 years old, with 80% of cases seen below 12 months. Eighty percent of CONS cases were seen in those younger than 12 months, while the remaining 20% were seen in 11-15-year-old-adolescents. All *Salmonella enteritidis* cases were seen in children below 12 months old.

Among neonates, 66.7% of infections were due to gram-negative bacilli, while the remaining 33.3% were caused by gram-positive cocci such as Group B Streptococcus (GBS), oxacillin-resistant *Staphylococcus aureus* (ORSA), and coagulase-negative staphylococci (CONS). Both of the GBS cases (100%) were seen in neonates. Other than Hib, Salmonella, and meningococcus, four gram-negative bacilli (*Acinetobacter* spp., *Proteus mirabilis, Serratia marcescens and Enterobacter cloacae*) caused late-onset neonatal sepsis/meningitis, while three other gram-negative organisms (*Pseudomonas aeruginosa, E. coli, and Klebsiella pneumoniae*) were seen among infants between 1-11 months. All three (100%) meningococcal cases were seen in infants less than 1 year of age.

There were eleven (14.9%) presumed *Mycoplasma pneumoniae* infections, based on a positive serum Mycoplasma IgM result. The majority (54.5%) were seen in the 5-10-year-old age group.

The most common clinical manifestation of bacterial meningitis was fever (81.1%), with a mean duration of 5.7±12.2 days. Majority (64%) of afebrile cases were in neonates, whose most common manifestations were respiratory distress (40%), seizures (26.7%), bulging fontanel (26.7%) and poor feeding (20%). Across all ages, the more commonly seen clinical manifestations were seizures (48.7%),

vomiting (29.7%), neck stiffness (23%) and bulging fontanel (20.3%). Cranial nerve palsies were observed in 10.8% of cases, with cranial nerves IV, VI and VII being more frequently affected. Of the 11 presumed *Mycoplasma pneumoniae* meningitis cases, 4 (36.4%) had respiratory symptoms such as cough (27.3%) or cough with colds (9.1%) on admission.

Table 2. Summary of CSF and Blood Test Results for Bacterial, Viral, Tuberculous and Fungal Meningitis Cases admitted from January 1, 1997 to August 31, 2017 (n=127)

	Bacterial Meningitis (n=74)	Viral Meningitis (n=34)	Tuberculous Meningitis (n=27)	Fungal Meningitis (n=2)
CSF				
WBC count (WBC/µL)	2043±9057 (range: 1-12,240)	50.9±179.6 (range 1-945)	163.8±180.2 (range: 0-651)	77±17
Lymphocytes (%)	36.2±34.3	39±37.1	65.2±38.9	73±17
Neutrophils (%)	46±37.5	19.3±24.3	11.8±16.4	4±4
Protein (mg/dL)	248.6±405.1	77.6±73.9	300±365.6	63.9±4.9
Glucose (mg/dL)	40.7±64.9	66.1±20.3	47.2±29.1	4.5±0.5
Blood				
WBC ($x10^3$/µL)	16.8±10.2	11.5±5.4	11±3.2	5.8±0.8
Lymphocyte (%)	27.4±17.7	44.6±29.4	25.8±16.9	20±16
Neutrophil (%)	62.3±20.1	50.3±27	64.2±19.4	58±6

For all cases of bacterial meningitis, cerebrospinal fluid analysis showed elevated mean WBCs with neutrophilic predominance, elevated protein, and low normal mean glucose. Blood tests showed elevated WBC counts, with neutrophilic predominance (see table 2).

For presumed *Mycoplasma pneumoniae* meningitis, CSF analysis showed a mildly elevated mean WBC (33.3±41.8 WBC/µL, range 0-99) with lymphocytic predominance (43.3±44% lymphocytes, 3.1±3.8% neutrophils), mildly elevated protein (77.7±38.9 mg/dL) and normal glucose levels (72.1±13.9mg/dL). Blood tests showed mildly elevated WBC counts (13.4±5.6x103/µL), with neutrophilic predominance (67.8±19.4% neutrophils, 22±15.4% lymphocytes). CRP was done in 43 cases (51.8%) and 36 (86%) had elevated results.

Computed tomography scan was the most commonly used imaging modality (59.5%), followed by ultrasound (21.6%) and MRI (17.6%). The most common abnormalities found on CT scan were leptomeningeal enhancement (31.8%), subdural effusion (18.2%), infarct (15.9%) and hydrocephalus (15.9%). Leptomeningeal enhancement (23.1%) and infarct (23.1%) were the most common MRI findings. Hydrocephalus was seen in 62.5% of cases where ultrasound was done. CT scan and MRI results were normal in 22.7% and 23.1%, respectively.

The most common complication of bacterial meningitis was recurrent seizures (36.5%), followed by hydrocephalus (14.9%) and subdural effusion (13.5%).

The most commonly used antibacterial agents were ceftriaxone (24.3%), penicillin G (14.9%) and chloramphenicol (13.5 %). Combination therapy was more common in the neonatal age group, where cefuroxime-amikacin and cefotaxime-amikacin were started in 33.3% and 13.3% of cases respectively. Once the diagnosis of meningitis was evident, cefuroxime-amikacin was shifted to the following antimicrobials: meropenem (40%), cefotaxime (20%) , ampicillin (20%) or a combination cefipime-amikacin (20%) Corticosteroids was used in 31.1% of cases.

The mean length of hospital stay was 18.3 days. Majority (54.1%) of patients were fully recovered upon discharge, while 31.1% were

discharged with neurologic deficits, the most common of which were weakness (6.8%), developmental delay (6.8%), seizure disorder (5.4%), hearing loss (4.1%) and lateral rectus palsy (4.1%).

Viral Meningitis

For viral meningitis, one (2.9%) case of Herpes simplex virus (HSV) infection was confirmed by CSF PCR. Majority (97.1%) of cases were not microbiologically confirmed.

Seven (20.6%) cases of presumed HSV 1 or 2, and one (2.9%) case of presumed dengue meningitis were recognized based on compatible clinical and laboratory findings and positive HSV-1 or -2 and dengue virus IgM and IgG serology, respectively. One case of presumed measles (2.9%) and mumps (2.9%) meningitis was identified based on clinical manifestations. There was one (2.9%) presumed Epstein-Barr virus case that manifested with prolonged fever of two weeks, weakness, loss of speech, headache and a positive EBV IgG serology.

Fever, with a mean duration of 5.52 ± 4.91 days, was seen in all cases (100%). Other associated symptoms were seizures (44.1%), headache (44.1%), neck stiffness (23.5%) and cranial nerve palsies (20.6%), with cranial nerves VI and VII being the most commonly involved.

CSF analysis showed a slightly elevated mean WBC and protein with lymphocytic predominance, with normal mean glucose findings. CBC showed a normal WBC (see table 2). C-reactive protein (CRP) was done in 15 (44.1%) cases and only 5 (33.3%) had elevated levels.

CT scan and MRI were done in 47.1% and 32.4% of cases respectively. CT scan was normal in 81.3% of cases. The most common CT scan abnormality was leptomeningeal enhancement (18.8%). The most common MRI findings as described were hyper intensities (36.4%), meningoencephalitis/encephalitis (27.3%) and leptomeningeal enhancement (18.2%). Cranial ultrasound was done in 3 (8.8%) cases, with findings of atrophy (100%) and hydrocephalus (33%).

The most common complications were recurrent seizures (20.6%) and weakness (17.7%), acute disseminated encephalomyelitis (ADEM) (11.8%), and pneumonia (11.8%).

The most common antimicrobial agent used was acyclovir (38.2%) followed by ceftriaxone (26.5%), and chloramphenicol (11.8%). Eleven patients (32.4%) received steroids. Antibiotics were started on some cases as empiric treatment until the diagnosis of viral meningitis became evident.

The mean length of hospital stay was 11.9 days. Majority (55.9%) of cases were discharged completely recovered. Residual morbidities noted in 32.4% of patients included seizure disorder (45.5%), spasticity/decorticate posturing (18.2%) and respiratory failure (9.1%).

Tuberculous Meningitis (TBM)

Among 17 TBM cases, only 3 (17.6%) were confirmed by either CSF TB culture or CSF TB PCR. The remaining 82.4% were diagnosed as probable TBM.

The most common manifestations of TBM were fever (100%), neck stiffness (52.9%), seizures (52.9%), headache (47.1%), vomiting (47.1%), cough (41.2%), and a positive Kernig (35.3%) and Brudzinski sign (29.4%). Cranial nerve palsy was seen in 23.5% of cases.

CSF analysis showed an elevated mean WBC with lymphocytic predominance, elevated mean protein, and low normal glucose levels (see table 2). The complete blood count showed normal mean WBC counts with neutrophilic predominance. C-reactive protein determination was done for all, and was elevated in 70.6% of cases.

Fourteen (82.4%) had a CT scan done, with the most common findings being hydrocephalus (71.4%), basal enhancement (50%), and infarct (28.6%). Only one (5.9%) patient had an MRI, which showed hydrocephalus, basal enhancement and

infarct. Three cases (17.6%) had an ultrasound done, showing hydrocephalus.

The most common complications were recurrent seizures (100%) and hydrocephalus (64.7%) and 23.5% of cases needed surgical intervention.

The most common treatment was a combination of isoniazid, rifampicin, pyrazinamide and ethambutol (76.5%). Streptomycin was added to the standard regimen in the rest of the cases (23.5%). Nine cases (52.9%) received steroids.

The mean length of hospital stay was 14.1 days. Eight cases (47.1%) were discharged completely recovered while eight cases (47.1%) went home with residual morbidity, the most common of which were weakness (17.7%) and lateral rectus palsy (11.8%).

Fungal Meningitis

Two patients had confirmed fungal meningitis where *Cryptococcus neoformans* and *Candida parapsilosis* were isolated.

Fever was the most common clinical manifestation (100%), followed by headache (50%), vomiting (50%), cranial nerve palsies (50%) and weakness (50%).

Cerebrospinal fluid findings showed elevated mean WBCs with 17±17% lymphocytes, 4±4% neutrophils, elevated protein, and markedly decreased glucose. The mean blood WBC was normal, with neutrophilic predominance (see table 2). CRP was elevated in both cases.

MRI was done in one case (50%), and showed restricted diffusion of the posterior-superior parietal cortical regions, with a consideration of encephalitic changes. The complications noted were subdural effusion (50%) and pneumonia (50%). Fluconazole (50%) and amphotericin B (50%) were used in these cases. Methylprednisolone was used in one patient (50%). The mean length of admission was 20 days. Both patients were discharged with residual neurologic morbidity, such as weakness (4/5 MMT on all extremities in 50% of cases) and diplopia (50%).

Fever Duration and Etiology

The Kruskal-Wallis Test results showed that at least two etiologies differed in the median fever duration in days (p=0.0001). Based on Dunn's Test, the median fever duration for viral meningitis cases was statistically shorter than those with TB and longer than those with bacterial meningitis (p=0.0001 and 0.0195, respectively). Furthermore, the median fever duration of TBM cases was statistically longer than those with bacterial meningitis (p<0.0001).

Fungal meningitis, due to its small sample size, was excluded in this and in other subsequent analyses.

Length of Hospital Stay

The Kruskal-Wallis Test results showed that at least two etiologies differed in the median length of stay (LOS) (p= 0.0008). Based on Dunn's Test, the median LOS for viral meningitis was statistically shorter than those with TB and bacterial meningitis (p=0.0127 and 0.0001, respectively). The difference in the median LOS for TB and bacterial meningitis cases was not statistically significant (p=0.3374).

Mortality Rate

The overall mortality rate was 10.2%. The mortality rates for bacterial and viral meningitis were 12.2% and 11.2%, respectively. No mortalities were seen for fungal and TB meningitis.

DISCUSSION

Male predilection and the first peak at 1 to 11 months of age observed in this study mirror the national demographics[15]. The second age peak at 5 to 10 years, which was common for viral and probable *Mycoplasma pneumoniae* infections, may be secondary to increased exposure to infectious agents coincident with school entry[16]. The WHO, PCMC and this study's findings are comparable, with 80%[17,] 87.5%[18]and 80% of all Hib meningitis cases

found in children less than 1-year-old. In this study, all cases of Salmonella infection occurred in children under 1 year old, similar to the findings of Owusu-Ofari (2003), who reported that 89.7% of Salmonella spp meningitis cases occurred in infants less than one year.[19] This study's finding of neonatal meningitis being due to gram-negative bacilli in 66.7% and gram-positive cocci in 33.3% of cases is similar to that reported by Morelos and Gatchalian, in which 70% of the pathogens were gram-negative bacilli and 30% were gram-positive cocci[20]. Neonates are particularly vulnerable to gram-negative infections, as neonatally-produced IgMs and maternally transmitted IgGs are less efficient against these organisms[3,16]. Mycobacterium tuberculosis infections are most likely to progress to disease in children younger than five years old, with the risk for disseminated disease being highest in infants.[8]

There was only one (2.9%) laboratory-confirmed case of HSV meningitis identified in this study. Laboratory confirmation of viral meningitis requires either the CSF culture or the viral PCR to be positive. The former has a low sensitivity (<10%)[21] while the latter was not available in the earlier years of this study's duration.

Fever was frequently present across etiologies, and was significantly longer in TB compared to bacterial and viral meningitis. A sub-acute to chronic clinical course and cranial nerve palsies were seen more often in tuberculous infection[22]. The neonates in this study presented with non-specific signs and symptoms, congruent with the findings of a local retrospective study by Morelos and Gatchalian[20].These underscores the need for prompt lumbar puncture and CSF analysis for this subset.

In this study, pleocytosis was highest in bacterial meningitis with CSF WBC counts as high as 12,960/µL. Taken in combination with CSF neutrophilic predominance, a bacterial cause should be highly suspected[23,24].

CSF protein may be elevated in any inflammation or infection caused by any organism, but is usually more elevated in bacterial and TB meningitis, as seen in this study. CSF protein elevation in TBM may be more pronounced due to blood brain integrity breach and gamma globulin synthesis on site[25].

One of the most frequently documented neuroimaging finding in this study was hydrocephalus, which when acquired, is most commonly caused by meningitis[26]. The combination of basal enhancement, hydrocephalus and infarct is specific for TBM[8] similar to the findings of Paguia et. al (2011)[27].

Ceftriaxone as monotherapy was the most commonly used drug in this study. Ceftriaxone constitutes the standard empiric therapy for community-acquired bacterial meningitis as it covers for *Streptococcus pneumoniae*, *Hemophilus influenzae* type b, *Neisseria meningitidis* and Salmonella spp. A local study by Saiton, Jr. (2004) compared ceftriaxone to ampicillin and chloramphenicol for the treatment of Hib meningitis. Patients treated with ceftriaxone had a 62% cure rate compared to 33% and 89% for ampicillin and chloramphenicol respectively. The lowest resistance was seen with ceftriaxone (<10%) and chloramphenicol (<10%), when compared to ampicillin (31%)[18].

Steroids, particularly dexamethasone was used in majority of cases in this study. A Cochrane trial on dexamethasone demonstrated that its use reduced the risk of severe hearing loss (6% from 9.3%), any hearing loss (13.8% from 19%), and neurologic sequelae (17.9% from 21.6%) signficantly[28]. It specifically impacted hearing loss in Hib infections in high-income countries, and decreased the mortality rate for *Streptococcus pneumoniae* and TBM by 6.1% and 25%, respectively[28,29].

Across all etiologies, recurrent seizures were the most common complication documented in this

study. The most common early neurologic complications of bacterial meningitis were seizures (36.5%), hydrocephalus (13.9%) and subdural effusion (13.5%)[30]. These findings were similar to those of Namani et. al. (2012), where subdural effusion was the most common complication of bacterial meningitis, followed by seizures and hydrocephalus[30]. In this study, hydrocephalus was present in 64.7% of children with TBM. This was similar to the findings of Raut (2013) who reported hydrocephalus in about 65% of patients and was associated with a worse prognosis[31].

This study showed no mortality for TB and fungal meningitis. This is contrary to reports from a local and an Indian government tertiary hospital, where mortality rates of 16-23.4% were seen in TBM[8,32]. The private, full-service, tertiary care setting where this study was done might have contributed to the lower mortality rates. The mortality rate for bacterial meningitis was 12.2%, which was close to the findings of Penaflorida and Garcia in 2012.[33]

CONCLUSION AND RECOMMENDATION

The different types of meningitis shared common symptomatology, including fever, seizures, vomiting, headache and neck stiffness. TBM, however, had the longest fever duration with the most frequent cranial nerve involvement. In bacterial meningitis, CSF pleocytosis was marked except for presumed *Mycoplasma pneumoniae* infection, which had a low mean WBC. The combined findings of leptomeningeal enhancement, hydrocephalus and infarct were unique to TBM. Ceftriaxone was the most commonly used antibiotic for bacterial meningitis, except for neonates for whom the combination of cefuroxime-amikacin was the most common initial regimen used, until microbiologic confirmation was available. Acute disseminated encephalomyelitis (ADEM) was unique to viral meningitis, while hydrocephalus was was more frequent and more severe in TBM. The shortest hospital stay and the highest full recovery rate were seen in viral meningitis.

Epidemiological, clinical and ancillary findings, when taken together, provide important clues to the pathogen and subsequent appropriate treatment for suspected pediatric meningitis cases.

A limitation of this study is the completeness and correctness of first-hand data which were dependent on clinician's entries in the reviewed charts, and which were not uniformly consistent in quality and quantity. Despite this, the setting in which the study was conducted, being a tertiary hospital with a high-volume of patients, makes its findings generalizable to a greater population. The researcher recommends further exploration of specific findings generated from this study.

REFERENCES

1. Department of Health. (2014). Philippine Health Statistics 2001-2010: Leading causes of child mortality. Department of Health. Philippines. Retrieved May 10, 2017 from www.doh.gov.ph
2. Philippine Pediatric Society. (2017). Committee on Registry of Childhood Disease (ICD-10). Retrieved May 10, 2017, from Philippine Pediatric Society, Inc: www.pps.org.ph.
3. Pediatric Infectious Disease Society of the Philippines (PIDSP), & Child Neurology Society of the Philippines (CNSP). (2015). Philippine clinical practice guidelines on the diagnosis and management of acute bacterial meningitis. *Pediatric Infectious Diseases Society of the Philippines Journal*, *Vol 16*(No.2), 2–42.
4. Waites, K., & Talkington, D. (2004). Mycoplasma pneumoniae and its role as a human pathogen. *Clinical Microbiology Reviews*, *17*(4), 697–728.https://doi.org/10.1128/CMR.17.4.697_728.2004
5. Logan, S. A. E., & MacMahon, E. (2008a). Viral meningitis. *BMJ*, *336*(7634), 36–40. https://doi.org/10.1136/bmj.39409.673657.ae
6. Michos, A. G., Syriopoulou, V. P., Hadjichristodoulou, C., Daikos, G. L., Lagona, E., Douridas, P., … Theodoridou, M. (2007). Aseptic Meningitis in Children: Analysis of 506 Cases. *PLoS ONE*, *2*(8), e674. https://doi.org/10.1371/journal.pone.0000674
7. Lee, L. V. (2000). Neurotuberculosis among Filipino children: an 11 years experience at the

Philippine Children's Medical Center. *Brain and Development*, *22*(8), 469–474. https://doi.org/10.1016/s0387-7604(00)00190-x

8. Philippine Pediatric Society, Inc. Committee on Handbook on Childhood Tuberculosis. (2016). *Tuberculosis in infancy and childhood* (4th ed.). Philippines: Philippine Pediatric Society, Inc.
9. Marais, S., Thwaites, G., Schoeman, J. F., Török, M. E., Misra, U. K., Prasad, K., … Marais, B. J. (2010). Tuberculous meningitis: a uniform case definition for use in clinical research. *The Lancet Infectious Diseases*, *10*(11), 803–812. https://doi.org/10.1016/s1473-3099(10)70138-9
10. Varzaneh, F., & Rezael, N. (2013). Cranial nerve palsy in tuberculous meningitis versus acute bacterial meningitis. *Acta Medica Iranica*, *51*, 661–662.
11. Moghtaderi, A., Alavi-Naini, R., & Rashki, S. (2013). Cranial nerve palsy as a factor to differentiate tuberculous meningitis from acute bacterial meningitis. *Acta Medica Iranica*, *51*(2), 113-118. Retrieved from http://acta.tums.ac.ir/index.php/acta/article/view/4480
12. Guo, L., Liu, L., Liu, Y., Chen, T., Li, S., Yang, Y., & Liu, G. (2016). Characteristics and outcomes of cryptococcal meningitis in HIV seronegative children in Beijing, China, 2002–2013. *BMC Infectious Diseases*, *16*(1). https://doi.org/10.1186/s12879-016-1964-6
13. Hung, J, Ou, L, & Huang, J. (2005). Central nervous system infections in patients with systemic lupus erythematosus. *The Journal of Rheumatology*, 32 (1). 40-43)
14. Huang, K.-Y., Huang, Y.-C., Hung, I.-J., & Lin, T.-Y. (2010). Cryptococcosis in Nonhuman Immunodeficiency Virus-Infected Children. *Pediatric Neurology*, *42*(4), 267–270. https://doi.org/10.1016/j.pediatrneurol.2009.10.015
15. Republic of the Philippines Department of Health (2017). Acute meningitis-encephalitis syndrome surveillance cases January 1 to April, 2017. Retrieved fromhttp://www.doh.gov.ph/sites/default/files/statistics/2017_AMES_W1_13.pdf retrieved November 20, 2017
16. Kliegman MD, R. M., Stanton MD, B. M. D., st. Geme MD, J. S., & Schor MD PhD, N. F. (2015). *Nelson Textbook of Pediatrics, 2-Volume Set*. Philadelphia: Elsevier Health Sciences.
17. Cedeño-Burbano, A. A., Galeano-Triviño, G. A., Manquillo-Arias, W. A., & Muñoz-García, D. A. (2016). Salmonella enteritidis meningitis in an infant: Case report and literature review. *Revista de La Facultad de Medicina*, *64*(3), 575. https://doi.org/10.15446/revfacmed.v64n3.54613
18. Saiton,Jr.,T. (2004). A retrospective cohort study comparing cure rates of chloramphenicol, ampicillin and chloramphenicol combination, and 3rd generation cephalosporin as initial antibiotic therapy for invasive Hib infections. *Pediatric Infectious Diseases Society of the Philippines Journa*l, 14 (1), 34-41 Retrieved from www.pidsphil.org
19. Owusu-Ofori, A., & Scheld, W. M. (2003). Treatment of Salmonella meningitis: two case reports and a review of the literature. *International Journal of Infectious Diseases*, *7*(1), 53–60. https://doi.org/10.1016/s1201-9712(03)90043-9
20. Morelos, A. M., & Gatchalian, S. R. (1996). Clinical profile of meningitis among Filipino neonates: A twelve-year collaborative review. *Pediatric Infectious Diseases Society of the Philippines Journal*, 1 (1) ,24-27
21. Caliendo, A. (2017). PCR testing for the diagnosis of herpes simplex virus in patients with encephalitis or meningitis. UpToDate. Retrieved from https://www.uptodate.com/contents/pcr-testing-for-the-diagnosis-of-herpes-simplex-virus-in-patients-with-encephalitis-or-meningitis
22. Lee, S.-A., Kim, S.-W., Chang, H.-H., Jung, H., Kim, Y., Hwang, S., … Lee, J.-M. (2018). A New Scoring System for the Differential Diagnosis between Tuberculous Meningitis and Viral Meningitis. *Journal of Korean Medical Science*, *33*(31). https://doi.org/10.3346/jkms.2018.33.e201
23. Negrini, B., Kelleher, K. J., & Wald, E. R. (2000). Cerebrospinal Fluid Findings in Aseptic Versus Bacterial Meningitis. *Pediatrics*, *105*(2), 316–319. https://doi.org/10.1542/peds.105.2.316
24. Águeda, S., Campos, T., & Maia, A. (2013). Prediction of bacterial meningitis based on cerebrospinal fluid pleocytosis in children. *The Brazilian Journal of Infectious Diseases*, *17*(4), 401–404. https://doi.org/10.1016/j.bjid.2012.12.002
25. Shekhar, R. (2013). CSF proteins as discriminatory markers of tubercular and pyogenic Meningitis. *Journal of Clinical and Diagnostic*

Research. https://doi.org/10.7860/jcdr/2013/6361.3226

26. Warf, B. C. (2005). Hydrocephalus in Uganda: the predominance of infectious origin and primary management with endoscopic third ventriculostomy. *Journal of Neurosurgery: Pediatrics*, *102*(1), 1–15. https://doi.org/10.3171/ped.2005.102.1.0001
27. Paguia,M.R., Laya, B.F., De Jesus, J.M., & Piedad, R.O. (2011). Accuracy of established CT scan findings in the diagnosis of cranial tuberculosis. *St. Luke's J Med*,2011;7:33-42
28. Brouwer, M. C., McIntyre, P., Prasad, K., & van de Beek, D. (2015). Corticosteroids for acute bacterial meningitis. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.cd004405.pub5
29. Prasad, K., Singh, M. B., & Ryan, H. (2016). Corticosteroids for managing tuberculous meningitis. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.cd002244.pub4
30. Namani, S. A., Koci, B. M., Milenković, Z., Koci, R., Qehaja-Buçaj, E., Ajazaj, L., … Ismaili-Jaha, V. (2012). Early neurologic complications and long-term sequelae of childhood bacterial meningitis in a limited-resource country (Kosovo). *Child's Nervous System*, *29*(2), 275–280. https://doi.org/10.1007/s00381-012-1917-3
31. Raut, T., Garg, R. K., Jain, A., Verma, R., Singh, M. K., Malhotra, H. S., … Parihar, A. (2013). Hydrocephalus in tuberculous meningitis: Incidence, its predictive factors and impact on the prognosis. *Journal of Infection*, *66*(4), 330–337. https://doi.org/10.1016/j.jinf.2012.12.009
32. Israni, A. V., Dave, D. A., Mandal, A., Singh, A., Sahi, P. K., Ranjan, R. D., & Shah, A. (2016). Tubercular meningitis in children: Clinical, pathological, and radiological profile and factors associated with mortality. *Journal of Neurosciences in Rural Practice*, *07*(03), 400–404. https://doi.org/10.4103/0976-3147.181475
33. Penaflorida, A. & Garcia, R.D. (2012). Clinical profile of children aged 0-18 years of age diagnosed with bacterial meningitis at a tertiary care center from 2001 to 2011. Makati Medical Center [unpublished]

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Montaña CM, Ong-Lim AI & Camposano JA.Clinical Profile, Microbiology, Management, and Outcome of Pediatric Brain Abscess at the University of the Philippines- Philippine General Hospital: A 5-Year Retrospective Study (2012-2016)

ORIGINAL ARTICLE

CLINICAL PROFILE, MICROBIOLOGY, MANAGEMENT, AND OUTCOME OF PEDIATRIC BRAIN ABSCESS AT THE UNIVERSITY OF THE PHILIPPINES - PHILIPPINE GENERAL HOSPITAL: A 5-YEAR RETROSPECTIVE STUDY (2012-2016)

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

ABSTRACT

Objective: To determine the clinical profile, microbiology, management, and outcome of pediatric brain abscess at a tertiary hospital in the Philippines from 2012 to 2016.

Methods: A retrospective study and review of medical records of 50 patients aged 18 years old and below diagnosed with brain abscess from 2012 to 2016 was performed.

Results: Majority of patients affected were 10 years old and below (74%), with no gender predilection, and mostly underweight/wasted (68%). Coverage for common vaccine-preventable pathogens was low (38% for *H. influenzae* type b, 2% for *S. pneumoniae*). Most common signs and symptoms on admission were fever (62%), vomiting (50%), and headache (50%). The top pre-disposing condition was congenital heart disease (46%), mostly Tetralogy of Fallot (33%). Methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated in 38%) of cases. Sterile cultures comprised 68% of cases. There were two cases of tuberculous abscess. Empiric antibiotics administered for patients seen in 2012 were penicillin G and chloramphenicol, with a shift to a third-generation cephalosporin and metronidazole in the succeeding years. Aspiration with or without drainage was performed in majority of cases (85%). Six underwent complete excision and had a shorter mean length of stay of 57 days, and a lower morbidity rate of 17% with no mortalities. The overall mean length of hospital stay was 65 days. Residual neurologic deficit was observed in 28%, mostly extremity weakness. Mortality rate was 6.8%. No statistical association was found between a predisposing condition and affectation of a particular area of the brain using the Fisher exact test.

Conclusion: There should be a high index of suspicion for brain abscess among patients with pre-disposing conditions (i.e. paracranial infection, cyanotic congenital heart disease) presenting with fever, headache, and vomiting. Common etiologic agents in this study were MRSA and Enterococcus. The isolates were sensitive to the antibiotics recommended for empiric therapy, particularly parenteral third generation cephalosporin + metronidazole for 6 to 8 weeks. Patients with sterile cultures were also continued on this regimen. With the high resistance rates to oxacillin, vancomycin should be considered for abscesses arising from paracranial infections and for those with breaks in the skull post-trauma. There was an overall reduction in mortality due to improved imaging studies and identification of pathogens for definitive treatment, as well as improved surgical techniques over time. A considerable number of affected children however had neurologic deficits upon discharge.

KEYWORDS: *Pediatric brain abscess*

INTRODUCTION

Brain abscess is a focal, intracerebral infection that begins as a localized area of cerebritis and eventually ends in a collection of pus surrounded by a well-vascularized capsule[1]. Seeding to the brain occurs by hematologic transit of microbes from contiguous site infections (e.g. chronic otitis), disruption of the pulmonary vascular bed which filters out bacteria (e.g. cyanotic congenital heart disease), direct inoculation after penetrating head injury or neurosurgical procedure, or from a cryptogenic source[1,2]. A high index of suspicion commonly arises from a good review of possible predisposing conditions such as paracranial infections, history of head trauma, or presence of congenital heart disease. Management of brain abscesses pose a challenge in clinical practice, owing to its complex bacteriology, as well as changing patterns of antibiotic resistance. In our setting, the problem is further confounded by the presence of sterile cultures brought about by late microbiologic testing and delay in surgery, which usually occurs several weeks into treatment. Antibiotic therapy with source control thru immediate surgery (aspiration, drainage, or excision), and management of associated complications are the mainstays of treatment.

Indirect seeding to particular areas within the brain has been postulated to be largely dependent on the underlying predisposing condition. For brain abscess that is not associated with direct inoculation thru instrumentation or trauma, this study explored a possible association between the location of the lesion and the predisposing condition.

Although brain abscess is a relatively uncommon condition owing to the protection provided by the impermeable blood-brain barrier, a significant percentage of children who recover have residual deficits including epilepsy, permanent sensory and motor deficits, visual defects, and personality changes[2]. Local mortality rates of children with brain abscess range from 4.8% to 12.8% based on studies done from 1990-1999[4,5].

This life-threatening condition calls for timely diagnosis and treatment. This study aims to aid the clinician increase his index of suspicion thru a better knowledge of common diagnostic and clinical features of brain abscesses. The nutritional and vaccination status of affected children, antimicrobial susceptibility patterns of isolates, response to local empiric antibiotics, and outcomes of children with brain abscess will be the focus of this paper.

MATERIALS AND METHODS

A retrospective study was performed by review of medical records of charity patients aged 18 years old and below, diagnosed with brain abscess from January 2012 to December 2016 at a tertiary hospital in the Philippines. In this institution, all pediatric patients diagnosed with brain abscess are referred to the Section of Pediatric Neurology, thus a list of patients diagnosed consecutively within this time period was generated from the monthly in-patient database of the Section of Pediatric Neurology. To verify completeness, supplemental data was gathered from the records of the Section of Infectious and Tropical Diseases in Pediatrics, which also co-manages patients with this diagnosis.

After excluding patients with extra parenchymal pus collection (intraventricular, subdural, or epidural empyema), a total of 80 patients diagnosed with intraparenchymal brain abscess remained. Several attempts were made to completely gather patient records for data analysis, but despite such efforts, only 50 charts were retrieved from the 80 identified cases.

To ensure the privacy of patients, names, addresses, hospital case numbers or other identifying data were excluded from the data collection sheets, and informed consent to access patient charts was requested to be waived in accordance with the Data Privacy Act of 2012 and the 2017 National Ethical Guidelines for Health-Related Research (NEGHHR).

Each patient was evaluated in terms of demographic data (age, gender, nutritional status using WHO Child growth standards, and vaccination coverage for *Haemophilus influenzae* type b and *Streptococcus pneumonia)*, clinical data (presenting signs and symptoms and co-morbidities), radiographic data (Cranial CT scan results), cultures and resistance pattern of isolates, antibiotic treatment regimen, surgical approach, and patient outcome (including residual neurological deficits on discharge). A definite diagnosis of brain abscess was made with the finding of a ring-enhancing lesion within the brain parenchyma via neuroimaging, or an intra-operative finding of intraparenchymal collection of pus[6]. Microbiologic cultures and imaging results were verified thru the records of the Department of Laboratories and Department of Radiology, respectively.

RESULTS

DEMOGRAPHIC DATA

There were 50 patients included in the study, 29 (58%) males and 21 (42%) females, with a male to female ratio of 1.4:1. The mean age of patients in this study was 7 years old, with a range

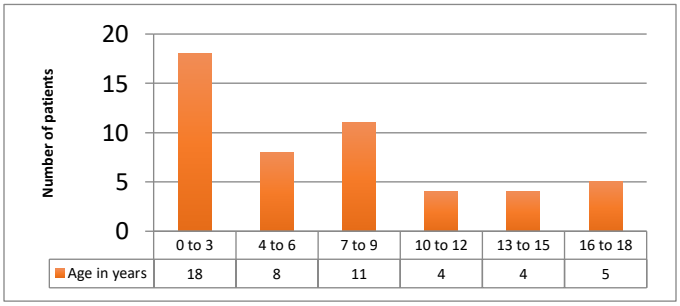

Figure 1. Age distribution of children with brain abscess (n=50)

of 2 months to 18 years old (Figure 1). Majority of patients were 10 years old and below (72%), and 36% (n=18) were < 3 years old.

NUTRITIONAL STATUS

Based on assessment of weight for length or height, majority of affected children were poorly nourished using the WHO growth curves as standard. Figure 2 shows that for the 41 patients with complete data, 36% were underweight, while 32% were severely underweight. Due to lack of data on length, the status of nine patients could not be assessed. However, these nine were all poorly nourished with a weight-for-age less than the 5th percentile using the CDC growth curve standards.

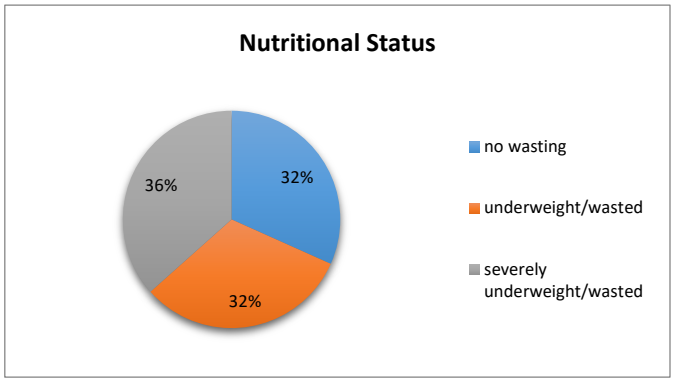

Figure 2. Nutritional status of children with brain abscess (n=41). As per WHO standards, underweight/wasted for z score below -2, severely underweight/wasted for z score below -3.

VACCINATION STATUS

Vaccination status was known in 66% of cases (n=33). Of these, only 19 patients received age-appropriate doses of *H. influenzae* type b (Hib) vaccine, and only one received age-appropriate doses of *S. pneumoniae* vaccine.

CLINICAL FEATURES

Presenting Signs and Symptoms

The classic triad of headache, fever, and focal neurologic deficit was seen in 28% of patients (n=14). The most common presenting symptom was fever in 62% followed by vomiting and headache, both seen in 50% of subjects. The most prominent neurologic symptom was vomiting, followed by altered state of consciousness, mostly drowsiness. Two (4%) came in stuporous. Seizure was mostly generalized (n=10, 20%), and only three patients came in with focal seizures (6%). The rest of the constitutional and neurologic signs and symptoms are listed in Table 1.

Table 1. Presenting signs and symptoms of children with brain abscess, (n=50).

Signs and Symptoms	Number of patients	Percentage (%)
I. Constitutional		
Fever	31	62
Headache	25	50
Poor appetite	6	12
Irritability	4	8
II. Neurologic		
IIa. Altered consciousness	24	48
IIb. Seizure	13	26
IIc. Meningeal signs	11	22
IId. Increasing head diameter	5	10
IIe. Increased intracranial pressure		
Vomiting	25	50
Papilledema	2	4
IIf. Focal Neurologic deficits		
Extremity weakness	12	24
Clonus	6	12
Facial asymmetry	4	8
Babinski	3	6
Limited Extraocular movement	3	6
Visual field defect	3	6
Spasticity	2	4
Loss of balance	2	4
Wide-based gait	2	4
Posturing	2	4
No verbal output	2	4
Dysmetria	1	2

PREDISPOSING CONDITION

The leading predisposing condition for brain abscess was uncorrected cyanotic congenital heart disease (46%), mostly Tetralogy of Fallot (22%). Other pathologies seen were Pentalogy of Fallot, double outlet right ventricle, tricuspid valve atresia, pulmonary valve atresia, and tricuspid valve atresia with pulmonary valve atresia and non-restrictive ventricular septal defect. There was one case of acyanotic heart disease - ventricular septal defect with chronic suppurative otitis media (CSOM).

Paracranial infections comprised 40% of cases leading to indirect seeding to the brain. Majority of these consisted of ear infections, followed by various types of oral and perioral infections. There was one case of nasal carbuncle, while another patient presented with scalp abscess.

Another distant site of seeding to the brain was the respiratory tract (n=3), with two cases of bacterial pneumonia and one case of sputum-positive pulmonary tuberculosis.

There were 5 cases which arose from direct inoculation. Three patients presented with traumatic brain injury, one patient presented with a retained foreign body, while another patient had a concomitant shunt infection. The primary source of infection was unknown in 5 cases.

Table 2. Predisposing condition in children with brain abscess.

Pre-disposing condition	Number of patients	Percentage (%)
I. Uncorrected Congenital Heart Disease	22	44
Tetralogy of Fallot	11	22
Pentalogy of Fallot	6	12
Double outlet right ventricle with ASD, VSD	2	4
Tricuspid valve atresia with non-restrictive ASD secundum, MAPCAS	1	2
Pulmonary valve atresia with myocardial sinusoids	1	2
Isolated ventricular septal defect	1	2
II. Paracranial infection	20	40
Ear infection	11	22
• Acute Otitis Media	9	19
• Chronic Otitis Media	1	2
• Otitis Externa	1	2
Oral infection	7	14
• Dental carries	6	12
• Peri-oral furunculosis	1	2
Nasal infection (carbuncle)	1	2
Scalp abscess	1	2
III. Distant infectious source		
Pulmonary infection	3	6
• Bacterial pneumonia	2	4
• Pulmonary tuberculosis	1	2
III. Direct inoculation and instrumentation	5	10
Intracranial Foreign Body (Metallic rod)	1	2
Traumatic brain injury secondary to fall	3	6
Ventriculoperitoneal shunt infection	1	2
IV. Cryptogenic (unknown)	5	10

**ASD Atrial septal defect; VSD Ventricular septal defect; MAPCAS Major aortopulmonary collateral arteries*

Table 2 shows the complete list of identified pre-disposing conditions for brain abscess in children.

RADIOLOGIC FEATURES

Cranial computed tomography (CT) scan was still the diagnostic imaging of choice, which manifests as a ring-enhancing lesion in the brain parenchyma. In majority of patients (n=29), multiple lesions were seen. The most frequently involved area of the brain was the parietal lobe, followed by the frontal and temporal lobe. Table 3 summarizes

the different areas of involvement as seen on imaging.

Majority of patients (96%) presented as surgical candidates on initial CT scan, with an aggregate abscess diameter >2.5 cm. The largest aggregate diameter documented was 7.8 cm, with a mean of 4.7 cm.

Table 3. Abscess location on initial cranial CT-scan.

Abscess location	Frequency	Percentage (%)
Parietal	26	52
Frontal	23	46
Temporal	19	38
Occipital	9	18
Cerebellar	7	14
Thalamus	2	4
Sellar-suprasellar	1	2

ASSOCIATION BETWEEN PREDISPOSING CONDITION AND ABSCESS LOCATION

No significant association was found between predisposing condition (excluding those from direct inoculation) and area of the brain affected using Pearson Chi, with a correction value using Fisher's exact test, with a level of significance of $p<0.05$ (Table 4).

Table 4. Association between predisposing condition causing indirect seeding to the brain and area of the brain affected using Pearson Chi and Fisher's exact test. Level of significance < 0.05.

Predisposing condition	Frontal	Temporal	Occipital	Parietal	Cerebellar	Thalamus	Sellar-suprasellar	Pearson chi p(X2)	Fisher's exact	p-value
Nasal infection	1	-	-	1	-	-	-	0.691	1.000	p>0.10
Ear infection	4	3	1	4	4	-	-	0.024	0.054	p>0.05
Oral infection	11	6	2	14	-	1	-	0.955	0.963	p>0.10
Scalp abscess	1	-	-	-	-	-	-	-	-	-
Pulmonary tuberculosis	-	-	-	-	-	-	1	-	-	-
Pneumonia	2	1	-	2	1	-	-	0.478	0.851	p>0.10
Congenital Heart Disease	9	9	3	13	1	1	-	0.656	0.639	p>0.10

MICROBIOLOGIC STUDIES

Specimen for abscess culture and sensitivity were obtained from 41 patients. Majority (68%) had no growth on aerobic cultures, and a microbiologic diagnosis was established in only 32% of cases (Table 5). The isolates were gram-positive bacteria, mainly Methicillin-resistant *Staphylococcus aureus* (MRSA) from patients with paracranial infections (nose and scalp) and breaks in the skull post-trauma.

Gram-negative isolates included *Proteus mirabilis*, Enterobacter spp., *Escherichia coli*, *Acinetobacter baumanii,* Pseudomonas *putida*, and *Klebsiella pnuemoniae*, and were mostly seen in patients with ear (CSOM) or shunt infection.

Only three of 13 cases had polymicrobial isolates consisting of combinations of Enterococcus spp + *Escherichia coli*, MRSA + *Acinetobacter baumannii*, and MRSA + Mycobacterium spp. (based on acid fast bacilli smear of abscess fluid).

Table 5. Microorganisms isolated from brain abscess fluid stratified according to pre-disposing condition.

**CSOM (Chronic suppurative otitis media), **Acid fast bacilli*

Organism Isolated	Frequency	Percentage	Associated condition(s)
Methicillin resistant Staphylococcus aureus (MRSA)	5	38	Nasal carbuncle Lip carbuncle Scalp abscess Traumatic brain injury
Enterococcus	2	15	Cryptogenic Tetralogy of Fallot with periodontitis Cryptogenic
Proteus mirabilis	1	8	CSOM*
Enterobacter	1	8	Traumatic brain injury with CSOM
Escherichia coli	1	8	Cryptogenic
Streptococcus viridans	1	8	Pentalogy of Fallot
Methicillin resistant Staphylococcus epidermidis (MRSE)	1	8	Traumatic brain injury
Acinetobacter baumannii	1	8	Nasal carbuncle
Pseudomonas putida	1	8	Cryptogenic
Klebsiella pneumoniae	1	8	Ventriculoperitoneal shunt infection
*Tuberculosis***	1	8	Pulmonary tuberculosis

(AFB) +1/30 on AFB smear of abscess fluid

The sensitivity and resistance pattern of isolates are shown in table 6. Notably, Staphylococcus isolates were 100% resistant to Oxacillin and Penicillin G. Majority of gram-positive isolates (MRSA, *Streptococcus viridans*, Enterococcus) were 100% susceptible to Vancomycin. Most gram-negative isolates were sensitive to Meropenem, Piperacillin-Tazobactam, and third generation Cephalosporins (Ceftriaxone, and Ceftazidime). Notably, one *Klebsiella pnuemoniae* isolate was multi-drug (extended

spectrum penicillin, cephalosporin, sulfonamide) resistant.

Table 6. Sensitivity and resistance pattern of isolates from brain abscess fluid in children.

Isolates	Type of resistance	Percent resistant	Susceptibility	Percent susceptible
Staphylococcus sp. (n=6)	Methicillin-resistant (MRSA, MRSE); Oxacillin and Penicillin G resistant	100 %	Vancomycin Ciprofloxacin	100% 33%
Gram positive (*Streptococcus viridans, Enterococcus sp.; n=3)*	—	—	Vancomycin	100%
Gram negative (*Acinetobacter baumannii, Proteus mirabilis, Enterobacter sp., Pseudomonas putida, Eschericia coli*; n=5)	Ceftazidime resistant Ceftriaxone resistant Ciprofloxacin	20% 20% 20%	Piperacillin-tazobactam Meropenem Ampillin-sulbactam Ceftriaxone Ceftazidime Gentamicin Ciprofloxacin Aztreonam	80% 80% 60% 60% 60% 60% 60% 40%
Klebsiella pnuemoniae (n=1)	Multi drug resistant (Piperacillin-Tazobactam, Ceftazidime, Trimetophrim-sulfamethoxazole resistant)	100%	Meropenem	100%

**Methicillin-resistant Staphylococcus aureus (MRSA)*
**Methicillin-resistant Staphylococcus epidermidis (MRSE)*

TREATMENT AND OUTCOMES

Medical Management

Empiric antibiotics prescribed for patients with brain abscess diagnosed in 2012 consisted of Penicillin G and Chloramphenicol. Subsequently in 2013, third generation cephalosporins (ceftazidime or ceftriaxone) combined with metronidazole, with or without an aminoglycoside (amikacin) were prescribed. Oxacillin was given for cases resulting from direct inoculation (post-surgical/post-traumatic). A 6 to 8-week course of directed therapy was given for microbiologically confirmed cases. For AFB smear positive cases, a 12-month regimen of anti-tuberculosis drugs, with 2HRZE 10HR, was started.

Surgical Management

The table below (Table 7) lists the different surgical procedures done on 39 patients. Abscess aspiration ± drainage was done in majority of cases (n=33). Only six patients underwent complete excision of abscess. Serial aspiration/drainage of abscess was done in five cases. As for the 11 remaining patients, surgery was deferred due to marked clinical improvement with significant decrease in abscess size on Cranial CT scan, no consent for surgery with subsequent decision to go home against medical advice, or mortality before the scheduled surgery.

Table 7. Surgical procedure performed on children with brain abscess, (n=39)

Surgical Procedure	Number of patients	Percentage
Complete excision	6	15
Aspiration and drainage		
Burrhole + Tube drainage	13	33
Craniectomy + Tube drainage	7	18
Needle drainage	1	3
Ultrasound guided aspiration	6	15
Marsupialization	1	3
Serial aspiration and drainage	5	13

OUTCOME

The mean reduction in the size of the abscess on discharge was 76%, while a complete resolution of the lesion was observed in eleven patients (22%) who were treated surgically with concomitant antibiotics (culture guided in 5 cases) for 6-8 weeks. Overall mean length of hospital stay was 65 days.

For those who underwent abscess aspiration ± drainage, mean length of hospital stay was 70 days, with a morbidity rate of 30%, and mortality rate of 6%. For the six patients who underwent complete excision of abscess, mean length of hospital stay was shorter at 54 days, morbidity rate was lower at 17%, with no mortalities.

Morbidity, defined as having residual neurological deficit on discharge, was seen in 14 patients (28%). Majority (50%) were observed to have extremity weakness, and almost one-third had epilepsy.

Table 8. Residual neurological deficits observed upon discharge, (n=14).

Neurological deficit	Number of patients	Percentage %
Epilepsy	4	29
Spasticity	2	14
Facial asymmetry	2	14
Extremity weakness	7	50
Slurred speech	1	7
Bitemporal hemianopsia	1	7
Pronator drift	1	7

Of the 44 patients who stayed on to complete treatment, three died, with a mortality rate of 6.8%. Two patients died of healthcare associated pneumonia, while one patient with shunt infection died of brain herniation from probable re-

accumulation of abscess. Six patients went home against medical advice.

DISCUSSION

Brain abscess, although uncommon in the pediatric age group, is a life-threatening condition that could progress rapidly, leading to devastating and permanent neurologic sequelae. A high index of suspicion, timely surgical intervention, and administration of appropriate antibiotics are essential in its management.

As in other studies focusing on children with brain abscesses[2,3,7], no gender predilection was seen. The predominant age group is comparable with findings from other studies[3,4,7,20] . Predilection of the disease for this age group may be partly explained by the higher prevalence of paracranial infections particularly ear infections with contiguous spread[20], as well as the <60% survival of children with critical congenital heart diseases up to 15 y/o[6].

As for contributory factors predisposing children to develop brain abscess, it was observed that a primary immunodeficient condition as well as secondary immunodeficient states such as $leukemia$[7] was not a common cause of brain abscess in local studies[3,4]. This study however supports the idea that a secondary immunocompromised state in the form of malnutrition can be a major risk factor for morbidity and mortality due to infectious agents. Strong associations between malnutrition and mortality from gastrointestinal and acute respiratory infections were reported [14,15], but its association with infections affecting the central nervous system is yet to be investigated. Leptin plays a central role in the speculated mechanism that connects nutrition and immunity. Under conditions of protein-energy malnutrition and low leptin concentrations, there is a decrease in the immune response in the form of decreased activation of naive T cells, memory T cells, and activation markers (CD69, CD25, and CD71)[16], as well as dysregulation of the hypothalamic-pituitary-adrenal axis with increase in serum levels of glucocorticoids, impairing macrophage function in animal studies[17].

As for protective factors, this study also supports the need to address vaccine preventable causes, and particularly immunize against *Streptococcus pneumoniae* and *Haemophilus influenza* type b (Hib)[4]. Studies on the brain abscess-specific protective effects of immunity against these pathogens is still lacking, but it is important to note that their protective effects on conditions which pre-dispose children to brain abscesses, particularly, pneumonia and middle ear infections is indisputable.

Similar to other studies, [3,4,10,15] the classic triad of fever, headache, and neurologic deficits was observed in less than 30% of children in this study. This is an observation, which may indicate that this triad is more specific, rather than sensitive in detecting brain abscess on initial presentation[19]. For the patients seen in this study, seizure on admission was mostly generalized rather than focal. This is in contrast to a study by Chuang in 2010, where seizures were mostly focal in 52% of cases, majority of which had solitary lesions[18]. The predominance of generalized seizures in this study may be explained by the fact that majority of cases had multiple lesions involving multiple lobes.

Previous studies have suggested that some predisposing conditions are associated with abscess predilection for particular areas of the brain. Infections arising from the middle ear, paranasal sinuses, and teeth presumably allows microbe transit thru the emissary veins serving these regions, explaining a tendency towards frontal lobe involvement for sinusitis and dental infection, and temporal lobe involvement in patients with chronic otitis and mastoiditis[1,8]. Infections associated with metastatic inoculation from distant extracranial sources (e.g. pulmonary infection, endocarditis), as well as conditions where there is disruption of pulmonary vascular bed filtration of bacteria (e.g. cyanotic congenital heart disease), tend to be associated with multiple cerebral abscesses, with a

distribution that reflects the regional cerebral blood flow of the middle cerebral artery[1,8]. The findings in our study are comparable to that of available local data[3,4], which showed no significant association between predisposing factor and the area of the brain affected. The lack of association however may be partly explained by the small sample size.

Most paracranial infections including post-traumatic inoculation, except that of the middle ear, were caused by Methicillin-resistant *Staphylococcus aureus*. This is in contrast with the study of Ablaza-Medalla et. al. done in the same institution in 1999, where most cases were caused by Methicillin-sensitive *Staphylococcus aureus*[4]. For patients with congenital heart disease, the isolates noted were Enterococcus and *Streptococcus viridans,* sensitive to Vancomycin, and cephalosporins (Cefepime or Ceftriaxone). Gram-negative organisms (*Escherichia coli*, *Pseudomonas putida, Proteus mirabilis*), were mostly sensitive to third-generation cephalosporins (ceftriaxone or ceftazidime) and carbapenems (meropenem), and were isolated from patients with infections of the middle ear, as with cryptogenic cases. These findings support the basis for subsequent change in the choice of empiric antibiotics from penicillin G to third generation cephalosporins in 2013. Only five cases had specimens sent for anaerobic cultures, and none of them had positive growths. Starting 2013, most patients were started on metronidazole than chloramphenicol, as the former has a better margin of safety with fewer side effects. By 2014, empiric antimicrobial coverage proposed by the institution's Section of Infectious and Tropical Diseases in Pediatrics (INTROP)[13] included a combination of third generation cephalosporin (ceftriaxone or ceftazidime) and metronidazole, with the addition of oxacillin in cases of head trauma, post-operative infections, or endocarditis.

What has remained constant is the high incidence of sterile cultures, with rates as high as 60%[12]. Notably in this study, 50% of those with negative cultures had previous antibiotic exposure, mostly intravenous cephalosporins, prior to surgical excision of the abscess. The practice of not routinely sending aspirates for anaerobic cultures may also be contributory. This parallels the local data where sterile cultures are reported in as many as 68% of cases, attributed to previous antibiotic intake and the inability to properly collect and culture for strict anaerobes[3,4,5].

In this study, patients with sterile cultures were evaluated for improvement following a regimen of empiric antibiotics (penicillin G + chloramphenicol, or ceftriaxone / ceftazidime + metronidazole), with the basis for improvement being clinical response and imaging studies. If after 14 days, imaging results did not show an interval decrease in the size of the abscess, escalation to meropenem was done and given for 6-8 weeks. With concomitant surgical intervention, interval decrease in size of the abscess was seen in 96% of patients with sterile cultures, with as much as 19-100% (mean of 66%) decrease from the largest aggregate diameter of the parenchymal lesion upon discharge.

A local study by Tongco and Domingo (1983) done in this same institution compared serial aspiration or drainage of pus from the abscess against total excision[9]. It was found that although total evacuation led to lower mortality rates, this was associated with an extended hospital stay. These findings were comparable to those in the present study, in terms of lower morbidity rate (17% vs 30%) and no mortalities (vs 2 mortalities). However, this study differs in terms of shorter mean length of hospital stay (54 vs 70 days) for those who underwent total excision compared to abscess aspiration ± drainage.

Comparable to other studies[5,12], morbidity, defined as having residual neurological deficit on discharge, was seen in 28% of patients in this study. Mortality rates prior to the 1980s ranged from 11-53%. Available data on local mortality between 1990-1998 [3,5] showed significantly lower rates, due to availability of improved imaging studies, microbiologic techniques for definitive treatment, as well as improvement in surgical techniques[1,2,11].

CONCLUSION

Brain abscess in children, although rare, is a life-threatening condition that requires prompt recognition, diagnosis, and treatment. There should be a high index of suspicion for this complication among patients with pre-disposing conditions (i.e. paracranial infections, cyanotic congenital heart disease), presenting with fever, headache, and neurological deficits. The likelihood of a brain abscess increases among patients with malnutrition, and among those who lack protection against vaccine preventable pathogens, such as *Streptococcus pneumoniae* and *Haemophilus influenza* type b (Hib). No significant association was found between predisposing condition and the area of the brain affected.

Organisms isolated in this study were sensitive to antibiotics recommended for empiric therapy[13], particularly parenteral third generation cephalosporins (ceftriaxone or ceftazidime) and metronidazole given for 6 to 8 weeks. Patients with sterile cultures were also continued on this regimen.

With the high rates of Methicillin-resistant *Staphylococcus aureus* (MRSA) in our present setting, vancomycin should be considered for abscesses arising from paracranial infections and for those with breaks in the skull post-trauma, with appropriate guidance from the infectious disease specialists. Optimal management calls for surgical evacuation, preferably complete excision of abscess. Morbidity and mortality rates decreased over time, which could be attributed to improved imaging studies, improved identification of pathogens for definitive treatment, as well as improved surgical techniques[1,2,11].

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REFERENCES

1. Saez-Llorens X, Guevarra JN. Parameningeal infections. In: Feigin RD, Cherry JD, Harrison GJ, Kaplan S, Steinbach WJ, Hotez PJ, editors. Textbook of Pediatric Infectious Disease 7th edition. Philadelphia: Saunders Elsevier; 2014, p462-468.
2. Fischer EG, McLennan JE, Suzuki Y. Cerebral abscess in children. American Journal of Diseases in Children 1981;135(8):746-749.
3. Palac-Tan E, Valdez NP, Martinez BS, Ferrer MT, Mejia AL. Brain Abscess in children: The NCH experience. Journal of the Philippine Medical Association 1992;68 (1):11-14.
4. Ablaza-Medalla CM, Oh D, Chua A, Salonga AM, Gatchalian SR. Brain abscess in children at the Philippine General Hospital: A prospective epidemiologic study. Pediatric Infectious Disease Society of the Philippines Journal 1999;4(1):15-21.
5. Dando N, Lukban M. Clinical features and outcome of brain abscess in infants and children (Philippine General Hospital, 1990-1996). Philippine Journal of Pediatrics 1998;4(3):195-199.
6. Oster M, Lee KA, Honein H. Temporal trends in survival among infants with critical congenital heart defects. Pediatrics 2013; 131(5):1502-1508.
7. Gon Lee C, Kang SH, Kim YJ, Shin HJ, Choi HS, Lee JH, Lee MH. Brain abscess in Korean children: A 15-year single center study. Korean Journal of Pediatrics 2010; 53(5):648-652.
8. Brook I. Brain abscess in children: microbiology and management. Journal of Child Neurology 1995;10(4): 283-288.
9. Tongco AD, Domingo FT. Surgical management of brain abscess: drainage or excision. Philippine Journal of Surgical Specialties 1983;38(2):100-104.
10. Ozsurekci Y, Kara A, Cengiz AB, Celik M, Ozkaya-Paralkay A, Karadag-Oncel E, Ceyhan M. Brain abscess in childhood: a 28-year experience. Turkish Journal of Pediatrics 2012;54(2):144-149.
11. Bonfield CM, Sharma J, Dobson S. Pediatric intracranial abscesses. Journal of Infection 2015; 71(S1):S42–S46.
12. Canpolat M, Ceylan O, Per H, Koc G, Tumturk A, Kumandas S, Ozturk MK. Brain abscesses in children. Journal of Child Neurology 2014;30(4):458–467.
13. Gatchalian S, Bravo L, Gonzales ML, Maramba-Lazarte C, Ong-Lim AL, Pagcatipunan M, Delos Reyes. Handbook of Pediatric Infectious Diseases 5th

edition, Manila: Section of Infectious and Tropical Diseases in Pediatrics (INTROP) 2014. p6-8.

14. Rodriguez L, Cervantes E, Ortiz R. Malnutrition and respiratory infections in children: A public health problem. International Journal of Environmental Research and Public Health 2011;8(4):1174-1205.
15. Yoon PW, Black RE, Moulton LH, Becker S. The effect of malnutrition on the risk of diarrheal and respiratory mortality in children <2 y of age in Cebu, Philippines. American Journal of Clinical Nutrition 1997;65(4):1070-1077.
16. Faggioni R, Feingold KR, Grunfeld C. Leptin regulation of the immune response and the immunodeficiency of malnutrition. The FASEB Journal 2002;15(14):2565–2571.
17. Monk JM, Makinen K, Shrum B, Woodward B. Blood corticosterone concentration reaches critical illness levels early during acute malnutrition in the weanling mouse. Exp Biol Med (Maywood) 2006;231(3):264–268.
18. Chuang M, Chang W, Chang H, Lin W, Tsai N, Hsieh M, Lu C. Predictors and long-term outcome of seizures after bacterial brain abscess. Journal of Neurology, Neurosurgery & Psychiatry 2010;81(8), 913–917.
19. Weinberg, G. Brain abscess. Pediatrics in Review. 2018;39 (5):270-272.
20. Beller AJ, Sahar A, Praiss I. Brain abscess: Review of 89 cases over a period of 30 years. Journal of Neurology, Neurosurgery, and Psychiatry 1973;36(5): 757–768.

CASE SERIES

INTRAVENTRICULAR ANTIMICROBIAL THERAPY IN CHILDREN WITH MULTI-DRUG RESISTANT VENTRICULITIS: A TERTIARY HOSPITAL EXPERIENCE AND LITERATURE REVIEW

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

ABSTRACT

BACKGROUND: Intraventricular antimicrobial therapy (IVT), defined as the direct installation of antimicrobial agents into the lateral ventricles has been utilized as the last therapeutic option for the treatment of multidrug-resistant ventriculitis. The aim of this case series is to report our institution's experience with IVT in pediatric patients with ventriculitis.

MATERIAL AND METHODS: Retrospective chart review was done. The demographic data, cerebrospinal fluid (CSF) culture isolates, treatment regimens, and clinical outcomes of these patients were collected and described.

RESULTS: Between 2016 to 2018, seven (7) pediatric patients diagnosed with ventriculitis caused by multidrug-resistant organisms underwent intraventricular antimicrobial therapy in combination with intravenous therapy. The median age was 1 year (range 1 month to 17 years old, mean: 4.4 years). Fifty-seven (57) percent of the patients were females. The isolated pathogens were *Acinetobacter baumannii* MDRO (n = 3), *Klebsiella pneumoniae* MDRO (n = 2), Methicillin-resistant *Staphylococcus aureus* (n = 1), and Methicillin-resistant *Staphylococcus epidermidis* (n = 2). One patient had mixed isolates on CSF culture (*Acinetobacter baumannii* and MRSE). The antimicrobial agents for IVT used were colistin (n = 4), vancomycin (n = 2), and gentamicin (n = 1). The mean time to initiation of intraventricular therapy from the diagnosis of ventriculitis was 19 days. The mean duration of IVT therapy was 15 days. The survival rate was 57%.

CONCLUSION: Ventriculitis caused by drug-resistant organisms is an emerging concern. Optimal therapy is not yet established and experience with IVT is limited. This series showed that there were no adverse effects related to IVT thus it may be considered an option for MDRO ventriculitis. Gram negative organisms are more common causes of ventriculitis in our institution.

KEYWORDS: *intraventricular IVT, ventriculitis, multidrug-resistant organism MDRO*

INTRODUCTION

Healthcare-associated ventriculitis is a type of deep incisional surgical site infection (SSI) from neurosurgery associated with significant mortality and long-term neurologic sequelae, prolonged hospital stay, and high burden of cost. [1,2]

Identified risk factors for healthcare-associated ventriculitis include presence of an external ventricular drain (EVD), duration of EVD placement exceeding 5 days, frequency of EVD manipulation for CSF sampling, drain irrigation, presence of intraventricular or subarachnoid hemorrhage, presence of cranial fracture with CSF leak, craniotomy, perioperative steroid use, and poor surgical technique.[4,5,6] In pediatric neurosurgical patients, the presence of a CSF shunt has particularly been identified as a risk factor for the development of SSI. In addition, other non-shunt-related neurosurgical procedures have also been identified, including myelomeningocoele closure, spine surgery/laminectomy, tumor excision, and epilepsy surgery. Other risk factors identified include female sex, development of pneumonia in the post-operative period, cerebral palsy, use of immunosuppressants, and emergency surgery. [1]

Gram-positive bacteria from skin flora, such as methicillin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci, account for almost 80% of the etiology of healthcare-associated ventriculitis. [7] However, multidrug-resistant gram-negative bacteria are increasingly becoming more prevalent, with *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and carbapenemase-producing Enterobacteriaceae being reported in literature as the most common pathogens. These organisms are associated with a higher morbidity and mortality especially in children due to limited treatment options.[2,8,9] Ventriculitis caused by fungi have been reported but generally account for only a small fraction of cases.[10]

Treatment of drug-resistant ventriculitis poses a challenge since choices of antimicrobial therapy are limited and response to standard intravenous antimicrobial therapy is generally poor.[11] For intravenous therapy to be effective, antimicrobial agents must be able to achieve and sustain adequate CSF concentrations. Ironically, ventriculitis is associated with less meningeal inflammation compared to meningitis, which can result in reduced antimicrobial penetration into the focus of infection. [12 13]

To address these concerns, non-conventional methods of treatment are now being utilized more frequently and IVT is one modality being used by physicians. It is necessary in patients with CSF shunt or drain infections that are difficult to eradicate with intravenous (IV) antimicrobial therapy alone, and is often utilized as the last therapeutic option for the treatment of multidrug-resistant and extensively drug-resistant organisms.[14] This route of administration bypasses the blood–CSF barrier, with controlled delivery of the antimicrobial agent to the site of infection. Intraventricular antimicrobials have the theoretical advantage of achieving high CSF concentrations without high systemic blood concentrations, hence lower potential systemic toxicities.[5] IVT antibiotic therapy can be delivered through Ommaya reservoir placement, ventriculostomies, or via direct ventricular puncture.[15,16] No standardized protocol for the treatment of CNS infection with intraventricular antibiotics has been established to date.[15]

This case series aims to describe our institutional experience with IVT in children diagnosed with ventriculitis caused by multidrug-resistant organisms, and to review literature on the use of IVT in children, duration of treatment, and adverse effects.

MATERIALS AND METHODS

This was a retrospective case series done at the Philippine General Hospital that included all pediatric patients below 19 years old diagnosed with multidrug-resistant ventriculitis who received IVT between 2016-2018. These patients were treated via IVT with an antimicrobial agent with

documented susceptibility, combined with intravenous antibiotic therapy. Cases that fulfilled the inclusion criteria were identified through a review of patient censuses. Electronic and hard copies of individual patient records were reviewed.

Cases were included based on a diagnosis of ventriculitis according to the following criteria: 1) positive CSF culture results, 2) CSF parameters consistent with ventriculitis, 3) clinical manifestations consistent with ventriculitis, and 4) a decision of the physician to treat as such.

The following data were obtained from patient records: demographic data; presence of underlying neurologic condition or congenital anomaly; results of CSF culture; treatment regimen and duration of IVT treatment. Outcomes were described as: cured, treatment completed, relapse and died. The time to initiation of IVT from the time of diagnosis of ventriculitis was also collected.

DEFINITION OF TERMS

Intraventricular antibiotic therapy (IVT) is defined as the direct installation of antimicrobial agents into the lateral ventricles.[5]

The 2018 CDC/NHSN surveillance definition of healthcare-associated meningitis/ventriculitis[3] must meet at least one of the following criteria:

1) organism(s) identified from cerebrospinal fluid (CSF) by culture or non-culture based microbiologic testing method

2) at least two clinical signs (fever > 38°C or headache, meningeal signs, or cranial nerve signs), and at least one of the following: increased white cells, elevated protein, and decreased glucose in CSF; organisms seen on gram stain of CSF; organisms identified from blood by a culture or non-culture based microbiologic testing method; or a diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for the organism.

For patients ≤ 1 year of age, clinical signs include fever > 38°C or hypothermia < 36°C, apnea, bradycardia, or irritability; meningeal signs; or cranial nerve signs.

Outcome definition as follows:

1) cured- negative CSF cultures, normalization of abnormal CSF parameters, resolution of clinical signs and symptoms, and completion of the intended duration of therapy

2) treatment completed- negative CSF cultures with resolution of signs and symptoms after completion of the intended duration of therapy, but without normalization of CSF parameters

3) relapsed- isolation of the same organism in the CSF or recurrence of abnormal CSF parameters with clinical symptoms, within 3 weeks of completing therapy for the initial episode[17];

4) died- death during the course of treatment, with or without documentation of resolution of infection.

RESULTS

Table 1. Demographic, clinical and treatment data of patients with multidrug-resistant ventriculitis

Patient	Age (yr)	Sex	CSF culture	Diagnosis	CNS device	IV antibiotics	IVT antibiotics	Duration of IVT (days)	Elapsed period before IVT (days)	IVT access	Outcome and Length of Hospital Stay
1	0.7	M	Methicillin-resistant *Stapylococcus aureus*	Congenital hydrocephalus secondary to aqueductal stenosis s/p ventriculoperitoneal shunt insertion	VPS	Vancomycin	Vancomycin 10 mg daily	23	33	External ventricular drain	Treatment completed (Discharged after 83 days)
2	1.0	F	Methicillin-resistant *Stapylococcus epidermidis*	Hydranencephaly s/p ventriculoperitoneal shunt insertion	VPS	Vancomycin	Vancomycin 10 mg daily	10	25	Ommaya reservoir	Treatment completed (Discharged after 147 days)
3	0.08	F	*Acinetobacter baumannii* MDRO	Chiari II malformation with ruptured lumbosacral meningocoele s/p lumbosacral meningocoele repair	None	Colistin, Ampicillin-Sulbactam	Colistin 125,000 IU daily	14	27	Ommaya reservoir	Relapsed (Discharged after 107 days, relapse of infection 1 week post-discharge, died)
4	7.0	F	*Acinetobacter baumannii* MDRO	Medulloblastoma s/p ventriculoperitoneal shunt insertion, gross excision of tumor	VPS	Colistin, Ampicillin-Sulbactam	Colistin 125,000 IU daily	10	11	External ventricular drain	Died (Intracranial bleed)
5	17.0	M	*Klebsiella pneumoniae* MDRO	Mixed germ cell tumor, s/p right frontal ventriculoperitoneal shunt insertion Intracranial hemorrhage secondary to tumor bleed, s/p shunt removal, left frontal tube ventriculostomy	VPS	Colistin, Meropenem	Colistin 125,000 IU daily	6*	1	External ventricular drain	Home per request (27 days)
6	0.33	F	Methicillin-resistant *Stapylococcus epidermidis*, *Acinetobacter baumannii*	Chiari II malformation, s/p lumbosacral meningocoele repair, ventriculoperitoneal shunt insertion	VPS	Vancomycin , Meropenem	Gentamicin 8mg daily	10	26	External ventricular drain	Cured (Discharged after 59 days)
7	5.0	M	*Klebsiella pneumoniae* MDRO	Medulloblastoma, s/p suboccipital craniectomy, excision of tumor, C1 laminectomy, ventriculoperitoneal shunt insertion	VPS	Colistin, Meropenem	Colistin 125,000 IU daily	30	10	External ventricular drain	Cured (Discharged after 126 days)

* treatment duration not completed

From 2016 to 2018, seven (7) pediatric patients diagnosed with ventriculitis caused by multidrug-resistant organisms had intraventricular antimicrobial therapy in combination with intravenous therapy (see table 1). The median age of patients who received combination intraventricular and intravenous therapy was 1 year (range 1 month to 17 years old, mean 4.4 years).

Fifty-seven (57) percent of the patients were females.

Four (4) patients underwent surgery for repair of a congenital CNS anomaly (1 case of congenital hydrocephalus, 1 case of hydranencephaly, and 2 cases of Chiari II malformation with lumbosacral meningocoele),

while 3 patients had surgery due to a CNS tumor (2 cases of medulloblastoma and 1 case of mixed germ cell tumor). Six of the 7 patients had shunt-related infections, while 1 patient developed infection related to lumbosacral meningocoele repair.

The isolated pathogens were *Acinetobacter baumannii* MDRO (n = 3), *Klebsiella pneumoniae* MDRO (n = 2), Methicillin-resistant *Staphylococcus aureus* (n = 1), and Methicillin-resistant *Staphylococcus epidermidis* (n = 2). One patient had mixed isolates on CSF culture (*Acinetobacter baumannii* and MRSE). Gram-negative bacteria accounted for 71% of all infections, while gram positive bacteria accounted for 43% of infections.

The antimicrobial agents used for IVT were colistin (n = 4), vancomycin (n = 2), and gentamicin (n = 1). In addition to IVT, IV antibiotics were given concurrently to all patients. In six of the seven patients, the same antibiotic was given intraventricularly and intravenously (see table 1.) The mean duration of IVT was 15 days (range of 6 to 30 days). The decision to start IVT was made on a case to case basis since there are no definite criteria to start IVT. But most of them were started due to the presence of MDRO in the CSF or repeated CSF culture positive results. The mean time to initiation of IVT from the diagnosis of ventriculitis was 19 days (range of 1 to 33 days). Twenty eight percent were cured (n = 2), and another 28% completed treatment and were discharged stable despite the presence of abnormal CSF parameters. One patient had an infection relapse and eventually expired while one patient died during treatment due to intracranial hemorrhage giving a 28% mortality rate for this case series. One patient went home against medical advise; sterilization of CSF was not documented in this patient. The overall survival rate was 57%.

DISCUSSION

We report seven pediatric patients diagnosed with post-operative multidrug-resistant ventriculitis treated with intraventricular antimicrobial therapy (IVT). IVT is increasingly becoming a therapeutic option in the management of multidrug-resistant ventriculitis poorly responsive to standard intravenous therapy. For an antimicrobial to work on CNS infections, it must achieve adequate CNS levels. This occurs via passage through the blood-brain barrier (BBB), which depends on the antimicrobial agent's physicochemical properties, including molecular weight, plasma protein-binding affinity, degree of ionization, and lipophilicity. Apart from these antimicrobial agent properties, another important consideration in the passage of antimicrobial agents through the BBB is the presence of meningeal inflammation. CSF penetration is improved via two mechanisms: 1) inflammatory mediators break down the BBB and increase permeability; and 2) the presence of meningitis causes a decrease in CSF production and outflow rates, leading to an increased CNS concentration and duration of time the antimicrobial agent remains in the CSF. Across the BBB, antimicrobial agents are transported via passive drug entry, facilitated diffusion, or active transport. Efflux pumps that actively transport antimicrobials out of the CNS also cause lower CSF concentrations; however, meningeal inflammation inhibits the activity of the efflux pumps, leading to higher CSF concentrations.

Efficacy and safety of intraventricular route of antibiotic administration have not been demonstrated in controlled trials, and antimicrobial agents are not approved by the US Food and Drug Administration for intraventricular administration, due to insufficient evidence to recommend their general use.[5] Despite the lack of sufficient evidence and standard protocol for IVT, the use of IVT in children has been reported in recent literature.[16,17,18,19,20,21,22]

The safety and efficacy of IVT antimicrobial therapy has been under constant debate. A Cochrane review on the use of intraventricular antibiotics for bacterial meningitis in neonates and older infants concluded that IVT with gentamicin in combination with IV antibiotics resulted in a three-fold increased risk for mortality, and the duration of

CSF culture positivity did not differ significantly compared to standard treatment with IV antibiotics alone. The poor outcomes in these patients were attributed to an increased endotoxin and interleukin-1 concentrations in the CSF of infants treated with IVT gentamicin, leading to further increase in inflammation.[23] In our series, only one patient received IVT gentamicin, a 4-month old female with Chiari II malformation who underwent lumbosacral meningocoele repair and ventriculoperitoneal shunt insertion, then developed ventriculitis with mixed isolates on CSF culture (Methicillin-resistant *Staphylococcus epidermidis* and *Acinetobacter baumannii*). This patient underwent shunt removal and was treated with 10 days of IVT gentamicin in combination with IV meropenem (duration of 23 days) and vancomycin (duration of 29 days). CSF studies post-treatment showed negative CSF culture and normal CSF parameters, hence patient underwent VPS reinsertion and was discharged improved with no adverse events noted during the entire duration of treatment. In contrast, one study reported focal seizures that lasted for more than one hour in a patient given IVT gentamicin (at a dose of 2mg/kg/dose) via EVD. The study did not provide the age of this patient, but only mentioned that their subjects were children ages 1 month to 16 years (mean ± SD: 23 ± 4 months). The seizures were controlled with IV phenobarbital maintained throughout the duration of IVT; treatment was discontinued for 24 hours and then restarted at a lower dose of 1mg/kg/dose with no recurrence of seizure episodes thereafter.[16]

Although the Cochrane review was specific for the use of IVT gentamicin particularly in neonates (69% of the studied population), other studies have reported the successful use of various antimicrobial agents for IVT in the neonatal population. One case report detailed the successful treatment of neonatal multidrug-resistant *Acinetobacter baumannii* ventriculitis in an 18-day old preterm infant (delivered at 34 weeks) using IVT polymyxin B.[24] In our series, the youngest patient was a newborn female diagnosed with Chiari II malformation with ruptured lumbosacral meningocoele who underwent meningocoele repair on the 5th day of life. The patient developed multidrug-resistant *Acinetobacter baumannii* ventriculitis on the 8th day of life, sensitive only to colistin. This neonate was initially treated with IV colistin and ampicillin-sulbactam, but persistence of the same organism on two succeeding CSF cultures warranted the addition of IVT colistin. This patient was treated with a total of 14 days of IVT colistin and 27 days of IV colistin and ampicillin-sulbactam that resulted in sterilization of the CSF. She was discharged improved, but was readmitted 1-week post-discharge due to purulent discharge at the shunt site. She was managed as a case of surgical site infection, treated with meropenem and vancomycin, but eventually expired due to septic shock from health-care associated sepsis. CSF parameters were abnormal but CSF culture was negative.

Six of the 7 patients developed device-related infection after surgery (infected ventriculoperitoneal shunts), while 1 patient had a non-device-related infection related to repair of a lumbosacral meningocoele. All patients with shunt-related infections underwent shunt removal and placement of an external ventricular drain that served as their access for IVT. The patient with non-device-related infection underwent Ommaya reservoir insertion that served as the IVT access.

In our series, gram negative organisms accounted for the majority of culture isolates (71%), compared to gram positive organisms (43%). One patient had mixed isolates on CSF culture, consisting of one gram negative and one-gram positive organism. Our results contrast that of various reports in literature where gram positive organisms prevail as the leading cause of ventriculitis. In the systematic review of 8 studies involving 86 patients with neurosurgical ventricular shunt infections by Drew et al., 46 patients had gram positive infections, 43 patients had gram negative infections. Mixed infections (gram positive and gram negative) were

described for four patients in the review, and one patient had a fungal infection. Of the 86 patients in that systematic review, 16 children were classified as refractory cases with multidrug-resistant organisms, defined as those who received second-line antimicrobial therapy following failed initial therapy. In these 16 children, there were 15 episodes of gram-positive organisms (majority of which are coagulase negative Staphylococcus species), and only 3 episodes of multidrug-resistant gram-negative organisms. It was not specified in the systematic review whether these refractory cases received IVT as part of their treatment regimen.[2] In another report by Arnell et al. of 34 episodes of CSF shunt infections in 30 children treated with systemic and intraventricular antibiotic therapy, gram positive organisms accounted for 29 episodes, while gram negative organisms accounted for only 5 episodes, with some patients having more than 1 infection.[19] The findings in this case series of gram negative organisms being more commonly isolated than gram positive in ventriculitis is important so that clinicians should include gram negative coverage when starting an empiric therapy.

Resistance rates of causative organisms identified in our series have been increasing or have remained high over recent years. The most recent national antimicrobial resistance surveillance data show that the cumulative MRSA rate is at 57%. For *Acinetobacter baumannii*, 42% of isolates tested against the full panel of antibiotics had a multidrug-resistant profile with combined resistance to aminoglycosides, carbapenems, fluoroquinolones, and sulbactam; only 23% of these isolates remained pan-susceptible. *Klebsiella pneumoniae* isolates have also been found to be more commonly resistant to multiple classes of antimicrobials, with up to 11% of isolates showing resistance to at least 2 or more classes of antimicrobials, such as penicillins (including beta-lactam and beta-lactamase inhibitor combinations), cephalosporins, aminoglycosides, carbapenems, fluoroquinolones, and trimethoprim-sulfamethoxazole.[25]

Dosages of antibiotic agents used for IVT may vary depending on the size or volume of ventricles, and on the volume of EVD output. The Infectious Diseases Society of America (IDSA) published the recommended dosages of common antimicrobial agents used for IVT, determined empirically based on the ability of the agent to achieve adequate CSF concentrations.[5] In our series, all dosages followed the IDSA recommendations. The IDSA also recommends CSF therapeutic drug monitoring to ensure that adequate CSF concentrations of antimicrobial agents are obtained. However, this was not done for any of the patients in this series due to limited resources.

To date, there is no existing consensus on the duration of IVT for drug-resistant ventriculitis. The shortest duration reported in literature is 1 day of IVT gentamicin in an adult with gram-negative ventriculitis, while the longest duration reported is 6 months of IVT levofloxacin and amikacin in a 25-year old male with multidrug-resistant *Mycobacterium tuberculosis* meningitis.[26,27] One retrospective report on treatment of shunt infections in children proposed an aggressive protocol where IVT is initiated at the onset of treatment upon removal of the infected shunt, and discontinued once the patient showed no further signs of infection and CSF culture is negative. The duration of IVT in this report was 6.2 ± 1.7 days, with no reported relapse in the long term follow up period (7.7 ± 3.6 years). This report concluded that shunt infections can be successfully treated with IVT without prolonged IV antibiotic courses and extended hospital stay.[16] In our series, the longest duration is 30 days of IVT colistin in a patient treated for *Klebsiella pneumoniae* MDRO ventriculitis and sepsis, who was cured and discharged stable with no relapse of infection on serial follow up.

Adverse events of IVT commonly reported in literature include chemical meningitis/ ventriculitis, seizures, and hearing loss.[28] In this case series, there were no reported episodes of seizures during the course of treatment of all patients. Hearing loss post-treatment was not assessed for these patients.

Chemical meningitis, the most commonly reported adverse event, poses a challenge for the physician to diagnose, as it is difficult to differentiate from progression of the ongoing infection or reinfection with a new pathogen due to multiple device manipulations. Forgacs et al. proposed specific clinical and CSF findings to distinguish chemical meningitis from a bacterial infection, and concluded that chemical meningitis can be differentiated from bacterial meningitis using their proposed criteria.[29] However, other authors have provided contradicting statements and have proposed to treat patients with clinical and laboratory features of post-operative meningitis as a bacterial infection, due to the high burden of morbidity and mortality from delays in initiation of therapy.[30] In this series, two patients demonstrated increasing CSF WBC counts and persistent low glucose concentrations but with sterile CSF cultures during the course of treatment. One patient was managed as a progressing infection, while another patient was diagnosed with a new-onset infection; antibiotics were shifted accordingly for both patients. None of the patients in this series were diagnosed to have chemical meningitis.

One patient in this case series showed a relapse in CNS infection after treatment. One patient, a 7-year old female diagnosed with medulloblastoma who underwent excision of tumor and VPS insertion, died of intracranial bleeding in the course of treatment for *Acinetobacter baumannii* MDRO ventriculitis with IVT colistin. The intracranial bleed was determined to have occurred as a complication of the underlying condition, and was not related to the treatment of the infection. The patient was on day 10 of IVT colistin at the time of demise; CSF cultures were already negative and other CSF parameters were improving. One patient, a 17-year old male diagnosed with mixed germ cell tumor with tumor bleed, underwent VPS insertion then developed *Klebsiella pneumoniae* MDRO ventriculitis. This patient was brought home per request of the family after 6 days of IVT colistin. Clinical improvement and resolution of infection were not documented in this patient, despite having the shortest time to initiation of IVT from the time of diagnosis of infection (1 day).

CONCLUSION

Ventriculitis caused by drug-resistant organisms is an emerging concern. Optimal therapy is not yet established and experience with IVT in this condition is limited, but IVT may be considered as a treatment option for ventriculitis caused by drug-resistant organisms. Well-designed, large-scale prospective studies are needed to determine the most effective IVT regimen, recognize adverse events, and monitor long-term patient outcomes.

REFERENCES

1. Sherrod BA, Arynchyna AA, Johnston JM, Rozzelle CJ, Blount JP, Oakes J, et al. Risk factors for surgical site infection following nonshunt pediatric neurosurgery: a review of 9296 procedures from a national database and comparison with a single-center experience. Journal of Neurosurgery: Pediatrics. 2017 April; 19(4). Available from:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5450913/pdf/nihms860363.pdf DOI: 10.3171/2016.11.PEDS16454.
2. Drew RJ, Cole TS, Lee MK, Paulus S, Mallucci CL, Riordan A. Antimicrobial treatment options for neurosurgical ventricular shunt infections in children from 1993 to 2012: a systematic review. Child's Nervous System. 2013 December. Available from:https://www.ncbi.nlm.nih.gov/pubmed/24322604 DOI: 10.1007/s00381-013-2333-z.
3. CDC/NHSN. CDC/NHSN Surveillance definitions for specific types of infections. National Healthcare Safety Network (NHSN) Patient Safety Component Manual. 2018 January. Available from:https://www.cdc.gov/nhsn/pdfs/pscmanual/pcsmanual_current.pdf.
4. Humphreys H, Jenks PJ. Surveillance and management of ventriculitis following neurosurgery. Journal of Hospital Infection. 2015. Available from: https://www.journalofhospitalinfection.com/article/S0195-6701(15)00051-1/fulltext DOI: 10.1016/j.jhin.2014.12.019.
5. Tunkel AR, Hasbun R, Bhimraj A, Byers K, Kaplan SL, Scheld WM, et al. 2017 Infectious Diseases Society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. Clinical

Infectious Diseases. 2017; 64(6): p. e34-e65. Available from:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5848239/pdf/ciw861.pdf DOI:10.1093/cid/ciw861.

6. Beer R, Lackner P, Pfausler B, Schmutzhard E. Nosocomial ventriculitis and meningitis in neurocritical care patients. Journal of Neurology. 2008; 255. Available from:https://link.springer.com/article/10.1007%2Fs00415-008-0059-8 DOI: 10.1007/s00415-008-0059-8.
7. Chen K, Wu Y, Wang Q, Wang J, Li X, Zhao Z, et al. The methodology and pharmacokinetics study of intraventricular administration of vancomycin in patients with intracranial infections after craniotomy. Journal of Critical Care. 2015; 30. Available from:https://www.sciencedirect.com/science/article/pii/S0883944114004031?via%3Dihub DOI: 10.1016/j.jcrc.2014.09.020.
8. Bargiacchi O, Rossati A, Car P, Brustia D, Brondolo R, Rosa F, et al. Intrathecal/intraventricular colistin in external ventricular device-related infections by multi-drug resistant Gram negative bacteria: case reports and review. Infection. 2014 April. Available from:https://link.springer.com/article/10.1007%2Fs15010-014-0618-0 DOI: 10.1007/s15010-014-0618-0.
9. Karaiskos I, Galani L, Baziaka F, Katsouda E, Ioannidis I, Andreou A, et al. Successful treatment of extensively drug-resistant Acinetobacter baumannii ventriculitis and meningitis with intraventricular colistin after application of a loading dose: a case series. International Journal of Antimicrobial Agents. 2013 February; 41. Available from:https://www.ijaaonline.com/article/S0924-8579(13)00070-8/fulltext DOI:10.1016/j.ijantimicag.2013.02.010.
10. Stenehjem E, Armstrong WS. Central nervous system device infections. Infectious Disease Clinics of North America. 2012; 26: p. 89-110. Available from: https://www.sciencedirect.com/science/article/pii/S089155201100081X?via%3Dihub DOI:10.1016/j.idc.2011.09.006.
11. 1Patel JA, Pacheco SM, Postelnick M, Sutton S. Prolonged triple therapy for persistent multidrug-resistant Acinetobacter baumannii ventriculitis. American Society of Health-System Pharmacists. 2011 August; 68. Available from:http://www.ajhp.org/content/68/16/1527.long?sso-checked=true DOI: 10.2146/ajhp100234.
12. Sullins AK, Abdel-Rahman SM. Pharmacokinetics of antibacterial agents in the CSF of children and adolescents. Pediatric Drugs. 2013; 15. Available from:https://link.springer.com/article/10.1007%2Fs40272-013-0017-5 DOI: 10.1007/s40272-013-0017-5.
13. Kumta N, Roberts JA, Lipman J, Cotta MO. Antibiotic distribution into cerebrospinal fluid: Can dosing safely account for drug and disease factors in the treatment of ventriculostomy-associated infections? Clinical Pharmacokinetics. 2017. Available from: https://link.springer.com/article/10.1007%2Fs40262-017-0588-3 DOI: 10.1007/s40262-017-0588-3.
14. Karaiskos I, Galani L, Baziaka F, Giamarellou H. Intraventricular and intrathecal colistin as the last therapeutic resort for the treatment of multidrug-resistant and extensively drug-resistant Acinetobacter baumannii ventriculitis and meningitis: a literature review. International Journal of Antimicrobial Agents. 2013. Available from: https://www.ijaaonline.com/article/S0924-8579(13)00054-X/fulltext DOI: 10.1016/j.ijantimicag.2013.02.006.
15. Mrowczynski OD, Langan ST, Rizk EB. Intra-cerebrospinal fluid antibiotics to treat central nervous system infections: A review and update. Clinical Neurology and Neurosurgery. 2018 May; 170: p. 140-158. Available from:https://www.sciencedirect.com/science/article/pii/S0303846718301896?via%3Dihub DOI: 10.1016/j.clineuro.2018.05.007.
16. James HE, Bradley JS. Aggressive management of shunt infection: Combined intravenous and intraventricular antibiotic therapy for twelve or less days. Pediatric Neurosurgery. 2008 January; 44: p. 104-111. Available from:https://www.karger.com/Article/Abstract/113111 DOI: 10.1159/000113111.
17. Cascio A, Mezzatesta ML, Odierna A, Di Bernardo F, Barberi G, Iaria C, et al. Extended-spectrum beta-lactamase-producing and carbapenemase-producing Enterobacter cloacae ventriculitis successfully treated with intraventricular colistin. International Journal of Infectious Diseases. 2014; 20: p. 66-67. Available from:https://linkinghub.elsevier.com/retrieve/pii/S1201-9712(13)00375-5 DOI:10.1016/j.ijid.2013.11.012.
18. James HE, Bradley JS. Management of complicated shunt infections: a clinical report. Journal of Neurosurgery: Pediatrics. 2008; 1. Available from: https://thejns.org/pediatrics/view/journals/jneurosurg-pediatr/1/3/article p223.xml?rfr_dat=cr_pub=pubmed&rfr_id=ori:rid:crossref.org&url_ver=Z39.88-2003 DOI:10.3171/PED/2008/1/3/223.

19. Arnell K, Enblad P, Wester T, Sjolin J. Treatment of cerebrospinal fluid shunt infections in children using systemic and intraventricular antibiotic therapy in combination with externalization of the ventricular catheter: efficacy in 34 consecutively treated infections. Journal of Neurosurgery: Pediatrics. 2007; 107. Available from:https://thejns.org/pediatrics/view/journals/j-neurosurg-pediatr/107/3/article-p213.xml?rfr_dat=cr_pub=pubmed&rfr_id=ori:rid:crossref.org&url_ver=Z39.88-2003 DOI: 10.3171/PED-07/09/213.
20. Jaspan HB, Brothers AW, Campbell AJP, McGuire JK, Browd SR, Manley TJ, et al. Multidrug-resistant Enterococcus faecium meningitis in a toddler: Characterization of the organism and successful treatment with intraventricular daptomycin and intravenous tigecycline. Pediatric Infectious Disease Journal. 2010 April; 29(4): p. 379-381. Available from:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4778705/pdf/nihms759305.pdf DOI:10.1097/INF.0b013e3181c806d8.
21. Remes F, Tomáš R, Jindrák V, Vaniš V, Šetlík M. Intraventricular and lumbar intrathecal administration of antibiotics in postneurosurgical patients with meningitis and/or ventriculitis in a serious clinical state. Journal of Neurosurgery. 2013 August. Available from:https://thejns.org/view/journals/j-neurosurg/119/6/article-p1596.xml DOI:10.3171/2013.6.JNS122126.
22. Turgut M, Alabaz D, Kocabas E, Erman T, Alhan E, Aksaray N. Cerebrospinal fluid shunt infections in children. Pediatric Neurosurgery. 2005; 41: p. 131-136. Available from:https://www.karger.com/Article/Abstract/85869 DOI: 10.1159/000085869.
23. Shah SS, Ohlsson A, Shah VS. Intraventricular antibiotics for bacterial meningitis in neonates. Cochrane Database of Systematic Reviews. 2012;(7). Available from:https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004496.pub3/full DOI: 10.1002/14651858.CD004496.pub3.
24. Mehar V, Zade P, Joshi M, Rajput N, Bhatambar G. Neonatal ventriculitis with multi drug resistant Acinetobacter baumanii: A case report and review of literature. Pediatrics and Therapeutics. 2012; 2(5). Available from:https://www.omicsonline.org/neonatal-ventriculitis-with-multi-drug-resistant-acinetobactor-baumanii-a-case-report-and-review-of-literature-2161-0665.1000131.php?aid=7714 DOI: 10.4172/2161-0665.1000131.
25. Antimicrobial Resistance Surveillance Reference Laboratory, Department of Health Research Institute of Tropical Medicine. Antimicrobial Resistance Surveillance Program (ARSP) 2017 Data Summary Report. 2017. Available from:http://arsp.com.ph/wpcontent/uploads/2018/07/2017_annual_report_summary.pdf.
26. Tangden T, Enblad P, Ullberg M, Sjolin J. Neurosurgical gram-negative bacillary ventriculitis and meningitis: A retrospective study evaluating the efficacy of intraventricular gentamicin therapy in 31 consecutive cases. Clinical Infectious Diseases. 2011; 52(11): p. 1310-1316. Available from:https://academic.oup.com/cid/article/52/11/1310/408246 DOI: 10.1093/cid/cir197.
27. Berning SE, Cherry TA, Iseman MD. Novel treatment of meningitis caused by multidrug-resistant Mycobacterium tuberculosis with intrathecal Levofloxacin and Amikacin: Case report. Clinical Infectious Diseases. 2001; 32: p. 643–6. Available from:https://academic.oup.com/cid/article/32/4/643/466248 DOI: 10.1086/318698.
28. Wang JH, Lin PC, Chou CH, Ho CM, Lin KH, Tsai CT, et al. Intraventricular antimicrobial therapy in postneurosurgical Gram-negative bacillary meningitis or ventriculitis: A hospital-based retrospective study. Journal of Microbiology, Immunology and Infection. 2014; 47: p. 204-210. Available from:https://ejmii.com/retrieve/pii/S1684118212002046 DOI: 10.1016/j.jmii.2012.08.028.
29. Forgacs P, Geyer C, Freidberg S. Characterization of chemical meningitis after neurosurgery. Clinical Infectious Diseases. 2001; 32(2): p. 179-185. Available from:https://academic.oup.com/cid/article/32/2/179/319157 DOI: 10.1086/318471.
30. Brown E, de Louvois J, Bayston R, Lees P, Pople I. Distinguishing between chemical and bacterial meningitis in patients who have undergone neurosurgery [Letters to the editor]. Clinical Infectious Diseases. 2002; 34. Available from: https://academic.oup.com/cid/article-pdf/34/4/556/23993107/34-4-556.pdf.