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EDITORIAL

TOIL AND DREAM ON

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The editorship came in as a big, BIG surprise. This with a bang and the news that our dear EIC (over the last 15 years), Dr. Cecilia Maramba-Lazarte will relinquish her post. The whole gamut of human emotions came into play as if I were this character Riley from "Inside Out"(Disney). I felt overly surprised. There was sadness, disgust, even fear. Anger? Angst? There was no perfect word to describe what it felt to be tasked to carry on and bring further "THE PIDSP JOURNAL".

For the past 22 years that the journal has existed (created in 1996), it has undoubtedly achieved its primary goal of providing Filipino clinicians local data which is relevant, timely, and essential in the management of pediatric infections. Since 2007, it became an online open access journal, making research results accessible and useful. Since 2009, articles submitted to the journal started to undergo the peer review process which ensured that only high-quality researches are published. In 2012, formal acceptance of the journal into the Western Pacific Region Index Medicus was achieved. With all these feats, what else is left to be done?

Being indexed with SCOPUS is a dream. It will increase the visibility of our local researches to the global audience and will give us an opportunity to collaborate with experts worldwide.

To say that Drs. Bravo and Maramba-Lazarte brought the PIDSP Journal to greater heights is an understatement. There was always a milestone achieved every 5 years. The last blast though in 2017 ended with an adieu (but not a sad one as Dr. Maramba-Lazarte remains to be an adviser). Could a blast in 2022 be a possibility?

Scopus? Dream On. For now, will take on this dream one step at a time. There is magic, but only with determination and hard work. We will continue to TOIL AND DREAM ON, and this with our fervent hope that you would continue to read on…

Pediatric Infectious Diseases Society of the Philippines Journal
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Cruz CR and Becina GT. Breastfeeding and Severe Pneumonia

ORIGINAL ARTICLE

ASSOCIATION BETWEEN BREASTFEEDING AND CLINICAL OUTCOMES OF INFANTS WITH VERY SEVERE PNEUMONIA

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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.

1st Place PIDSP Research Contest

ABSTRACT

Objective: To determine the association of breastfeeding with the clinical outcomes of infants with very severe pneumonia`.

Methods: This retrospective study included intubated, full-term infants between one to six months of age admitted for very severe pneumonia at the critical care units of the National Children's Hospital from 2005 to-2015. The 52 subjects per type of feeding (exclusively breastfed and non-exclusively breastfed) were selected using simple random sampling. We examined the association between the type of feeding with the length of ICU stay, ventilator days, health-care-associated infection (HAI) and mortality.

Results: A total of 104 infants were included in the study. The exclusively breastfed (EBF) infants stayed for a shorter amount of time in the ICU than the non-exclusively breastfed (NEBF) infants (p-value = 0.0067). The EBF infants had shorter intubation period and mechanical ventilation use (p value=0.001), and less HAI (p-value = 0.015). There were more infants with very severe pneumonia who died from the NEBF group but no significant association (p-value = 0.076) was found between mortality and the type of feeding.

Conclusion: Exclusively breastfed infants who were admitted for very severe pneumonia at the critical care areas showed better outcomes in terms of shorter ICU stay and ventilator use, and lower incidence of HAI as compared to the NEBF infants. However, data showed no significant association between mortality and type of feeding.

KEYWORDS:
Breastfeeding, very severe pneumonia,

INTRODUCTION

Breastfeeding and human milk are considered the normative standards for infant feeding and nutrition according to the American Academy of Paediatrics (AAP).[1-2] Breastfeeding also improves the infant and maternal health outcomes in both industrialized and developing world.[3] In the 2017 WHO fact sheet on infant and young child feeding, it was mentioned that over 820,000 of children under 5 years old could be saved yearly if all children 0-23 months were optimally breastfed.[4] Meanwhile, the 2012 Pneumonia and Diarrhea Report conducted by UNICEF stated that young infants who are not exclusively breastfed are at a greater risk of dying due to these two diseases. Infants who are not breastfed are 2 times more likely to have pneumonia and 15 times more likely to die from it than are exclusively breastfed children.[5]

Community-acquired pneumonia is a potentially serious infection in children that often results to hospitalization, and if severe, will require ICU admission.[6] Studies have shown that breastfeeding is a key intervention for reducing pneumonia morbidity and mortality during the first 23 months of life.[7] Meanwhile, non-breastfeeding or early cessation of breastfeeding increases the risk of acute lower respiratory tract infections and frequent hospitalization.[8-9] It also increases the incidence of hypoxemia and mortality in infants who have both pneumonia and diarrhea.[11-12]

Studies on breastfeeding in the Philippines are either on the practices and determinants of breastfeeding or factors affecting breastfeeding. Although there are local studies that show breastfeeding decreases morbidity and mortality of children from diarrheal and respiratory diseases[12], there is no study yet that shows the association of breastfeeding with that of the outcome of infant patients admitted for very severe pneumonia in critical care units of a hospital. This study aimed to determine whether breastfeeding has an association with improved health outcomes in infants, 1-6 months old, with very severe pneumonia.

Objective: This study aims to determine the association of breastfeeding with the clinical outcomes of infants with very severe pneumonia admitted at the Pediatric Intensive Care and Pulmonary Critical Care units from 2005 – 2015.

METHODS

This retrospective cohort analytical study determined the association of breastfeeding with the clinical outcomes of infant patients with very severe pneumonia in critical care units of a hospital. The baseline characteristics of exclusively breastfed and non-exclusively breastfed infants were compared according to gender, age, weight on admission, nutritional status, and baseline chest x-ray result. The clinical outcomes of infants in terms of length of ICU stay, mechanical ventilator days, the incidence of HAI and mortality were determined.

Study subjects were full-term infants, 1 – 6 months old admitted for very severe pneumonia in the Pediatric intensive care (PICU) and Pulmonary Critical care units (PCCU) of the National Children's Hospital from 2005 - 2015.

Inclusion criteria: Intubated term infants, 1-6 months old diagnosed with very severe pneumonia either directly admitted at the PICU/PCCU or admitted at the ward and transferred to any of the critical care units in less than 24 hours.

Patients who had major congenital abnormality or dysmorphic features likely to affect the life expectancy; major neurologic conditions; chronic respiratory disease (bronchopulmonary dysplasia); surgical (abdominal wall defects, short bowel syndrome) or medical (necrotizing enterocolitis) conditions

that need surgical intervention; and severe malnutrition were excluded.

Data that were collected from patients included the following: gender; age; gestational age at birth; maternal age; parity and illness during pregnancy; feeding history and duration of breastfeeding; weight upon admission; length and weight-for-length z-score; nutritional status upon admission; baseline chest radiography result; length of ICU stay; ventilation days; presence of healthcare-associated infection; and mortality. The treatment given for both groups were not taken into account. We assumed that patients were given standard regimen for very severe pneumonia.

Infants were grouped depending on their type of feeding, whether they are exclusively breastfed, or non-exclusively breastfed. Exclusive breastfeeding was defined in this study as no other food or drink, not even water, except breastmilk (including milk expressed or from a wet nurse) from birth up to day of discharge, even if patient is placed on NPO temporarily for medical indication/s, but allows the infant to receive ORS, drops, and syrups (vitamins, minerals, and medicines). Non-exclusive breastfeeding, on the other hand, was defined as either formula-feeding or mixed feeding.

The number of subjects to be included was computed using a 95% level of confidence and 80% power of the study. Fifty-two subjects per type of feeding—exclusively breastfed and non-exclusively breastfed, were enrolled in the study to detect a 20% reduction in infection. A similar ratio was used in the study of Patel, et al.[13]

Charts of 109 patients were reviewed. The subjects were grouped under two clusters: 54 subjects under exclusively breastfed, and 55 subjects under the non-exclusively breastfed. From each cluster, 52 patients were selected by simple random sampling using RAND function in Microsoft Excel.

Data analysis was based on the following tests: Mean and SD for age, admission weight, and length of ICU stay; Two-sample T-test with equal variances (for age, weight and length of ICU stay); and Fisher's exact test to examine the significance of association between two kinds of classification (for gender, nutritional status, duration of ventilator use, health-care-associated infection and mortality).

RESULTS

The infant's characteristics like gender, age, weight on admission, length, weight-for-length Z-score, and baseline chest radiography result were compared according to the type of feeding and shown in Table 1.

The mean age of exclusively-breastfed infants was 1 - 4 months old as compared to the mean age of the non-exclusively breastfed which was 1.5 – 5 months old. Using 5% significance, there was statistical significance between the ages of the two groups. The exclusively-breastfed group was younger (P-value = 0.037) than that of the non-exclusively breastfed group.

There was no significant difference (P value = 0.383) in the mean weights of both groups.

For nutritional status, 38 out of 52 (73%) exclusively breastfed infants and 39 out of 52 (75%) non-exclusively breastfed infants had normal nutritional status. There was noted more infants that were overweight in the exclusively breastfed group (10%) than that of the non-exclusively breastfed (6%), while there were less 'wasted' infants in the exclusively breastfed group (17%) than that of the non-exclusively breastfed (19%) group. However, the analysis showed that there was no significant difference (P value = 0.754) in the nutritional status of both groups.

Comparing the baseline chest x-ray, results showed that more infants in the non-exclusively breastfed group (27%) had complicated

pneumonia as compared to the exclusively breastfed infants (5.8%). Using a one-sided Fisher's exact test (P value=0.003), the exclusively breastfed group was found to have better x-ray results than the non-exclusively breastfed group.

Table 1. Comparison of Infants with Very Severe Pneumonia at NCH, 2005-2015 Baseline Characteristics According to Type of Feeding.

	EBF n = 52	NEBF n = 52	P value
Gender			
Female	28 *(53.8%)*	23 *(44.2%)*	0.327
Male	24 *(46.2%)*	29 *(55.8%)*	
Age (months)			
Mean±SD	2.461 (±1.540)	3.135 (±1.700)	0.037
Weight (kg)			
Mean±SD	4.877 (±1.187)	5.097 (±1.370)	0.383
Nutritional Status			
Normal	38 *(73%)*	39 *(75%)*	0.754
Overweight	5 *(10%)*	3 *(6%)*	
Wasted	9 *(17%)*	10 *(19%)*	
Baseline Chest X-ray Result			0.003
Uncomplicated Pneumonia	49 *(94.2%)*	38 *(73%)*	
Complicated Pneumonia	3 *(5.8%)*	14 *(27%)*	
Atelectasis	1	2	
Consolidation	2	6	
Effusion	0	4	
Pneumothorax	0	2	

Table 2 showed the comparison of infant's outcome according to the type of feeding. The mean length of ICU stay of exclusively breastfed infants was shorter or 5.654±2.930 days as compared with that of the non-exclusively breastfed group which was 8.143±6.503 days. There was a significant difference between the length of ICU stay of exclusively breastfed and non-exclusively breastfed infants (P-value =0.0067).

None of the exclusively breastfed infants was on a mechanical ventilator for more than 7 days, while 10 non-exclusively breastfed infants (19.2%) were on prolonged intubation. Based on this parameter, an association was established between the type of feeding and duration of ventilation (P value=0.001).

Of the 52 exclusively breastfed infants, only 1 had a healthcare-associated infection (HAI) (1.9%) as compared to the 8 (15.4%) infants from the non-exclusively breastfed group. This again showed that there was an association between HAI and type of feeding (P-value = 0.015).

Six (11.5%) infants died from the exclusively breastfed group while 13 (25%) died from the non-exclusively breastfed group. Despite a difference of 13% between the two groups, there was no significant association (P-value = 0.076) found between mortality and type of feeding at 5% significance.

Due to the significant difference in the baseline chest x-ray results between the two groups, a subgroup analysis was done to compare the outcome of infants whose chest x-ray only showed 'uncomplicated pneumonia' (Table 2b). A significant difference was still noted between the length of ICU stay of exclusively breastfed and non-exclusively breastfed infants (P-value =0.0162). The exclusively breastfed infants had a shorter duration of ICU stay than the non-exclusively breastfed infants. Also, NEBF group significantly stayed longer on the ventilator as compared to the EBF infants (P value=0.002). Data also showed that there was an association between HAI and type of feeding (P-value = 0.019). More infants from the NEBF group had HAI as compared to the EBF group. There was still no significant association (P-value = 0.352) between mortality and type of feeding at 5% significance.

Table 2. Comparison of Outcome According to Type of Feeding of Infants with Very Severe Pneumonia at National Children's Hospital, 2005-2015.

	EBF n = 52	NEBF n = 52	P value
Length of ICU Stay (days)			
Mean days ±SD	5.654 (±2.930)	8.143 (±6.503)	0.0067
Days on Ventilator			
> 7 days	0	10 *(19.2%)*	0.001
≤ 7 days	52 *(100%)*	42 *(80.8%)*	
Healthcare-associated infection (HAI)			
With HAI	1 *(1.9%)*	8 *(15.4%)*	0.015
Without HAI	51 *(98.1%)*	44 *(84.6%)*	
Mortality			
Died	6 *(11.5%)*	13 *(25%)*	0.076
Survived	46 *(88.5%)*	39 *(75%)*	

Table 2b. Comparison of Outcome According to Type of Feeding of Infants with Uncomplicated Pneumonia by Baseline Chest Xray at National Children's Hospital, 2005-2015.

	EBF n = 49	NEBF n = 38	P value
Length of ICU Stay (days)			
Mean days ±SD	5.65(±3.02)	7.93(±5.79)	0.0162
Days on Ventilator			
> 7 days	0	7 *(18.4%)*	0.002
≤ 7 days	49 *(100%)*	31 *(81.6%)*	
Healthcare-associated infection			
With HAI	1 *(2%)*	7 *(18.4%)*	0.019
Without HAI	48 *(98%)*	31 *(81.6%)*	
Mortality			
Died	5 *(10.2%)*	7 *(18.4%)*	0.352
Survived	44 *(89.8%)*	31 *(81.6%)*	

DISCUSSION

In this study, the association of breastfeeding with the outcome of infants 1-6 months old with very severe pneumonia admitted to a pediatric tertiary hospital from 2005-2015 was reported. Clinical outcomes namely: length of ICU stay, ventilation days, the incidence of healthcare-associated infections, and mortality rate, were compared between the

exclusively breastfed and non-exclusively breastfed groups.

The study by Patel and colleagues showed that low birth weight infants who were fed exclusively with human milk during their NICU stay were discharged earlier (11.7 days shorter) as compared to those infants who received exclusive formula milk.[14] A similar trend toward earlier improvement was seen in this research. This study showed that there was a significant difference between the lengths of ICU stay of EBF and NEBF infants. Data revealed that exclusively breastfed infants had approximately 2-5 days shorter stay in the Critical Care unit than the non-exclusively breastfed infants.

Another study by Patel showed that breastfeeding very-low-birth-weight infants greatly reduced the risk for acquiring sepsis by almost 20%; it also significantly lowered associated NICU costs by decreasing the likelihood of ventilator use.[13] The study of Tiewsoh and colleagues showed that children who were hospitalized for severe community-acquired pneumonia and were not exclusively breastfed had abnormal baseline chest x-ray results. They were also most likely to require a change of antibiotics from the primary regimen and had prolonged hospital stay.[15] Similarly, this study showed that the baseline chest x-ray results of infants in the non-exclusively breastfed group presented with more complicated pneumonia (x-ray findings of effusion, atelectasis, air leak/pneumothorax, and consolidation). The infants under this group also were on a mechanical ventilator for more than 7 days. This study also demonstrated that there was a significant association between healthcare-associated infection and type of feeding. According to studies, tracheal intubation is the most important risk factor for ventilator-associated pneumonia, which is the most common infectious complication among patients admitted to the ICU.[16] Although this study did not mention the type of the healthcare-associated infection, prolonged intubation among the non-exclusively breastfed infants in this study might have contributed to the increased incidence of HAI and subsequent prolonged length of ICU stay.

The study of Chen and Rogan showed that breastfed babies were 21% less likely to die between ages 1 month and 1 year, and that ≥ 3 months of breastfeeding showed fewer odds for dying in the post-neonatal period as compared to the ever/never breastfed.[17] Meanwhile, the study of Lamberti and his colleagues revealed that the relative risk of pneumonia mortality among 0-5 months of age was higher among never breastfed and partially breastfed infants as compared to the exclusively breastfed infants.[7] Likewise, this study showed that there were fewer infants with very severe pneumonia who died from the exclusively breastfed group (12%) as compared to the non-exclusively breastfed group (25%). Despite a difference of 13%, there was no significant association between mortality and type of feeding at 5% significance. However, this study compared only two groups of infants based on the type of feeding (exclusively breastfed versus non-exclusively breastfed); and those infants who were never breastfed, partially breastfed, and breastfed for at least 3 months were all included under the non-exclusively breastfed group. Comparing the mortality between 3 groups (never breastfed, infants who had exclusive breastfeeding for at least 3 months, and infants who had 6 months of exclusive breastfeeding) might have given a more significant result.

Since this is a retrospective cohort study, the baseline characteristics between the two groups were found to be significantly different when it comes to the severity of pneumonia as shown in their chest x-ray results. Hence, the

effect of non-exclusive breastfeeding to the duration of ICU stay, ventilator days, and incidence of HAI cannot be attributed to non-exclusive breastfeeding alone, since this group significantly had more complicated pneumonia by baseline chest x-ray. To account for this, a subgroup analysis comparing the outcomes of infants whose baseline chest x-ray only showed 'uncomplicated pneumonia' was done. Data still showed that exclusively breastfed infants had better outcomes in terms of length of ICU stay (P-value =0.0162), ventilator use duration (P value=0.002), and HAI (P-value = 0.019) as compared to the non-exclusively breastfed infants. There was still no significant association (P-value = 0.352) between mortality and type of feeding at 5% significance. Meanwhile, comparing the outcomes of those infants whose chest x-ray only showed 'complicated pneumonia' was not possible due to their small sample sizes.

CONCLUSION AND RECOMMENDATION

Exclusively breastfed infants with very severe pneumonia admitted at the critical care areas had better outcomes as compared to the non-exclusively breastfed infants in terms of shorter ICU stay and ventilator use, and lower incidence of healthcare-associated infection. This is the first local study that showed the association of breastfeeding with the outcome of infants aged 1-6 months old with very severe pneumonia admitted to the critical care unit. This research also revealed that more infants who were non-exclusively breastfed died; however, there was no significant association between mortality and type of feeding. With such results, this can serve as a tool in educating the parents on benefits of exclusive breastfeeding and can be used to promote breastfeeding.

One limitation of this study is that the treatment given for both groups were not taken into account. Another important limitation of this study is its retrospective study design. The researchers recommend a prospective study design so as to get a detailed feeding history, which was a problem encountered when this research was conducted. Since this study compared only two groups of infants per type of feeding, namely exclusively breastfed versus non-exclusively breastfed infants, the researchers recommend another study that will separate the "non-exclusively breastfed" group further into "never breastfed", and "exclusively breastfed for 3 months". This might give a more significant result in the association of breastfeeding and mortality. Also, in doing a prospective study, weight gain can be included as an outcome since the infant's weight can be taken and plotted daily. Maternal and infant factors that were not included in this study, like maternal age, education, and smoking history, and the infant's gestational age and birth weight, can be taken into account as baseline characteristics.

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Caysido ECL, Ganggangan F. and Runez R. Effect of Bovine Colostrum on ANC Acute Lymphocytic Leukemia PatientsUndergoing Chemotherapy

ORIGINAL ARTICLE

EFFECT OF BOVINE COLOSTRUM ON THE ABSOLUTE NEUTROPHIL COUNTS OF ACUTE LYMPHOCYTIC LEUKEMIA PATIENTS UNDERGOING CHEMOTHERAPY: A DOUBLE-BLIND RANDOMIZED PLACEBO-CONTROLLED STUDY

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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.

3RD Place, PIDSP Research Contest 2017.

ABSTRACT

Background: Changes in the blood cell counts, such as leukopenia and neutropenia, in patients with Acute Lymphoblastic Leukemia (ALL) are common events following chemotherapy. These commonly delay further administration of chemotherapeutic agents. Furthermore, the risk of infection rises correspondingly with the degree of neutropenia. Bovine colostrum is a rich source of immunoglobulins and other antimicrobial factors. These immunoglobulins are believed to improve the immune function and may be effective in the prevention of neutropenia following chemotherapy.

Objective: To determine the efficacy of bovine colostrum in preventing neutropenia among ALL patients undergoing chemotherapy.

Methods: This study included pediatric patients, aged 6 months to 18 years old diagnosed with ALL undergoing chemotherapy. Twenty-one subjects were randomly assigned to receive bovine colostrum or placebo that were taken twice a day for a week beginning from the first day of chemotherapy. Baseline complete blood count (CBC) and the absolute neutrophil count (ANC) were determined before and after 7 days of giving the colostrum or placebo. A t-test was applied to determine significant differences before and after the supplementation on each group.

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Results: Results showed that there was a significant increase in ANC of patients given bovine colostrum as compared to the placebo group with a p-value of 0.007. There were also significant increases in the white blood cells and platelet counts in those who were given bovine colostrum, with p-values of <0.001 and 0.001, respectively. No untoward effects were observed on both groups.

Conclusion: Bovine colostrum is effective in increasing the ANC of ALL patients undergoing chemotherapy and with no noted side effects.

KEYWORDS:
acute lymphoblastic leukemia (ALL), absolute neutrophil count, bovine colostrum

INTRODUCTION

Neutropenia is a common complication noted among ALL patients after chemotherapy. Chemotherapy-induced neutropenia typically occurs three-to-seven days after chemotherapy drugs are administered and continues for several days before recovering to normal levels.[1] Treatment for neutropenia depends on the cause. For chemotherapy-induced neutropenia, the usual strategy in recent years has been the injection with a man-made protein that is similar to the naturally occurring protein, granulocyte-colony stimulating factor (G-CSF). G-CSF is produced in the body by the immune system and stimulates the formation of neutrophils.[2] The injections are usually given shortly after the last treatment of a chemotherapy cycle and are continued until the desired ANC level, usually 1,000, is reached. However, its cost and availability limit the compliance of patients to the regimen hence a search for other remedies is warranted.

Bovine colostrum is a milk secreted during the first few days after calving and is a rich source of immunoglobulins and other antimicrobial factors.[3] These immunoglobulins are believed to improve the immune function and may be effective in treating immune system deficiencies and in the treatment of neutropenia. Bovine colostrum has shown some promise in different fields of medicine and has a lot of scope in the prevention and treatment of various illnesses including cancer in human beings.[4] There are limited data regarding the use of bovine colostrum in neutropenia and most are based on anecdotal reports. Dr. Dwyer in 2011 in the New England Journal of Medicine claims that "Immunoglobulin in colostrum has been used to successfully treat thrombocytopenia, anemia, neutropenia, and other conditions such as Myasthenia Gravis, Guillain Barre Syndrome, Multiple Sclerosis, Systemic Lupus, Rheumatoid Arthritis, Bullous Pemphigoid, Kawasaki Syndrome, Chronic Fatigue Syndrome and Crohn's disease".[3] On the other hand, a FactMed analysis in 2012 reported that 2 patients taking bovine colostrum developed neutropenia, however, this was not elaborated.[5] There have been no randomized trials to support these claims.

The objective of this study is to determine the efficacy of a one-week supplementation of bovine colostrum (Pro-Ig) in preventing neutropenia among patients with acute lymphocytic leukemia (ALL) undergoing maintenance chemotherapy.

MATERIALS AND METHODOLOGY

This randomized, double-blind, placebo-controlled trial involved pediatric ALL patients between the age of 6 months to 18 years undergoing chemotherapy using the standard protocol and was on the maintenance phase using mercaptopurine, methotrexate, vincristine, and prednisone. The study period was from February 2016 to September 2016.

The patients who met the following criteria were included in this study:

1. A baseline WBC of more than or equal to 2.8 x 10^9/L provided that the absolute neutrophil count is more than or equal to 1000.
2. A baseline hemoglobin of at least 100 g/L and a platelet count of at least 150 x 10^9/L
3. No other co-morbid illnesses like congenital heart disease, acute or chronic kidney disease and are not critically ill to be admitted to the intensive care unit or had an infection requiring antibiotic use.
4. No known allergy to dairy products.

5. Not presently taking other supplements/vitamins including bovine colostrum (Pro-Ig).
6. Either in-patient or outpatient.

Due to the limited number of ALL patients in this institution (2-4 cases of standard chemotherapy per month), the sample size was determined by total enumeration wherein, all patients satisfying the inclusion criteria were included in the study period of 8 months. All patients had informed consent. This study underwent technical review and approval by the hospital Ethics Review Committee.

The baseline values of the patients' complete blood count were obtained. Then the absolute neutrophil count (ANC) was computed by multiplying the WBC count with the neutrophils plus bands multiplied by 1000. (ANC = WBC X (neutrophils + bands) x 1000). Eligible participants were randomly assigned to either the treatment group or the placebo group by asking the parent or guardian to get a piece of paper from a box that contained the corresponding codes of the test products to be used. Each participant received either the bovine colostrum (Pro-Ig) or the placebo treatment and was blinded to the test product received. The bovine colostrum was manufactured by Essential International Ingredients Corporation, France distributed by Prebiotech Philippines. The placebo used contains starch and was similar in taste and appearance with the bovine colostrum. The test products were provided by Prebiotech Philippines. The identity of the test products was only obtained & revealed by the supplier after the statistical analyses have been made.

Upon enrollment, the resident-in-charge gave the corresponding test product that was picked by the patient or parent. In the package, an instruction, written in English and Filipino, on the proper administration of the test product was placed. The test products were to be dissolved in 2 tablespoons of water. The test products were taken orally, twice a day for 7 days (after breakfast & after dinner) under the supervision of the nurse on duty/and or parent/guardian for in-patients; and the guardian/parent for outpatients. The administration of the test products commenced on the first day of the standard maintenance chemotherapy treatment and daily thereafter, to complete the 14 doses before measuring the outcomes. As instructed, the participants collected the empty sachets and submitted them to the resident after the 7 days of treatment. Participants in this research were given 2 grams of colostrum per day. On the other hand, the placebo used contains pea starch. The test products were all tolerated.

After 7 days, complete blood count and platelet count were again measured using blood samples (0.5 ml if using aquisel microtainer tubes, or 2 ml if using EDTA tube) drawn from the patients' antecubital area. The blood tests were done at the same laboratory for all participants.

Statistical analysis:

Frequency distribution and percentage were used to describe the demographic data. Fisher's exact test was used to determine significant differences in the distribution proportion between treatment groups. Levene's test was used to compute and analyze the ANC and the CBC parameters to determine whether there are significant differences between the treatment groups before the intervention. Independent and dependent T-tests were conducted to compare the outcomes between two groups.

RESULTS

A total of 21 participants were enrolled in this study, 11 of which were randomized to the bovine colostrum group and 10 to the placebo group. All were able to complete the study. Eighty-six percent were below 10 years old and 66% were males.

Table 1. Demographic Profile and baseline CBC of bovine colostrum and placebo group (N=21)

PARAMETERS	Placebo Group(n=10)	Bovine Colostrum Group(n=11)	p-value*
a. Age			
1-9 y/o	8(38.1%)	10(47.6%)	
10 & Above	2(9.5%)	1(4.8%)	0.586
b. Sex			
Male	6(28.6%)	8(38.1%)	
Female	4(19.0%0	3(14.3%)	0.659
Hemoglobin	128.30	146.10	O.992
Hematocrit	0.38	0.44	0.472
WBC (x10^9/L)	6.00	5.68	0.307
Neutrophils (%)	0.70	0.61	0.974
Lymphocytes (%)	0.26	0.40	0.681
Monocytes (%)	0.03	0.02	0.405
Eosinophils (%)	0.02	0.04	0.066
Platelet Count (x 10^9/L)	382.50	316.1O	0.924
ANC	4215.49	3189.31	0.304

**significant @ p-value ≤ 0.05*
***expressed as mean values*

Table 1 shows that there is no significant difference in the demographics of both groups as indicated by the p-value of 0.586 and 0.659 for age and gender, respectively.

Using Levene's test, no significant difference was noted in the baseline CBC, ANC, & platelet count values of both groups as shown by the p values of more than 0.05.

Table 2. Pre- and Post-Treatment blood count values of the Placebo Group (n=10)

Variables	Pre Treatment Values	Post Treatment Values	Change from baseline		P*
			Mean	%	
Hemoglobin(g/L))	128.30	125.20	-3.1	-2.4%	0.225
Hematocrit (%)	0.38	0.37	-0.01	-2.63	0.290
WBC (x10^9/L)	6.00	5.63	-0.37	-6.17	0.555
Neutrophils (%)	0.69	0.60	-0.09	-13.04	0.045 *
Lymphocytes (%)	0.26	0.31	0.05	19.23	0.098
Monocytes (%)	0.027	0.024	-0.003	-11.11	0.771
Eosinophils (%)	0.019	0.051	0.032	168.42	0.045 *
Platelet Count (x10^9/L)	382.50	407.6	25.1	6.56	0.269
ANC	4,215.50	3,406.96	-808.5	-19.18	0.167

**significant @ p-value ≤ 0.05*
***expressed as mean values*

Table 2 shows that the hemoglobin, hematocrit, WBC, neutrophils, and ANC decreased after treatment in the placebo group, but only the neutrophils showed a significant decrease. Other CBC parameters, i.e. lymphocytes, monocytes and platelet count, showed no significant increase except for eosinophils.

Table 3. Pre- and Post-Treatment blood counts of the Bovine Colostrum Group (n=11)

Variables	Pre Treatment Values	Post Treatment Values	Change from baseline		P-value
			mean	%	
Hemoglobin (g/L)	132.82	120.27	-12.5	-9.45%	0.007*
Hematocrit (%)	0.397	0.36	0.037	-9.32%	0.003*
WBC (x10^9/L)	5.162	7.43	2.268	44.19%	<0.001 *
Neutrophils (%)	0.55	0.63	0.08	14.55	0.176
Lymphocytes (%)	0.36	0.32	-0.04	-11.11	0.355
Monocytes (%)	0.021	0.024	0.003	14.29	0.71
Eosinophils (%)	0.038	0.032	-0.006	-15.79	0.476
Platelet Count (x10^9/L)	287.36	378.O9	90.73	31.57	0.001*
ANC	2899.37	4561.19	1661	57.32	0.007*

**significant @ p-value ≤ 0.05*
***expressed as mean values*

Table 4. Mean changes in the CBC, platelet count and ANC values of both study groups (N=21)

Variables	Placebo Group			Bovine Colostrum			P-value*
	Pre Treatment	Post Treatment	Mean change %	Pre Treatment	Post Treatment	Mean change %	
Hemoglobin (g/L)	128.30	125.20	-3.1	132.8	120.2	-12.5	0.051
Hematocrit (%)	0.38	0.37	-0.01	0.397	0.36	-0.03	0.020*
WBC (x10^9/L)	6.00	5.63	-0.37	5.162	7.43	2.268	0.002*
Neutrophils (%)	0.69	0.60	-0.09	0.55	0.63	0.08	0.021*
Lymphocytes (%)	0.26	0.31	0.05	0.36	0.32	-0.04	0.099
Monocytes (%)	0.027	0.024	-.003	0.02	0.02	.003	0.644
Eosinophils (%)	0.019	0.051	.032	.038	.032	-.006	0.027*
Platelet Count (x 10^9/L)	382	406	25.1	287	378	90.7	.041*
ANC	4,215.50	3,406.96	-808	2899.37	4561.91	1661.82	0.003*

**significant @ p-value ≤ 0.05*
***expressed as mean values*

Table 3 shows that after treatment with bovine colostrum, the patients' hemoglobin and hematocrit decreased significantly; the lymphocytes also decreased but was not significant. The WBC, ANC, and platelet counts increased significantly after the administration of bovine colostrum. The increase in the neutrophils, monocytes of the patients were not significant.

Comparison of both groups after the treatment is shown in table 4. Both the hemoglobin and hematocrit decreased in both groups with the bovine colostrum group having the lower hemoglobin and hematocrit values but only the decrease in hematocrit was significant. The WBC and neutrophil values decreased in the placebo group (with a mean decrease of 0.37 and 0.09, respectively), while it increased in the bovine colostrum group, with a mean of 2.268 and 0.08, respectively. The mean increase in the platelet and ANC counts were significantly higher under the bovine colostrum group.

Both treatment groups did not experience any untoward event or side effect during the intervention until 7 days of follow up after the intervention.

DISCUSSION

Acute lymphoblastic leukemia is characterized by the overproduction and accumulation of cancerous, immature white blood cells known as lymphoblasts. It is most common during childhood, with a peak incidence at 2 to 5 years of age and slightly more common in males than in females as also seen in this study; the reason for this is still unknown.[6] Risk classification (such as standard-risk, high-risk, or very high-risk) is based on the age upon diagnosis and the initial white blood cell count.[7]

Standard chemotherapy or protocol for ALL consists of three phases: remission induction, intensification (consolidation), and maintenance therapy along with central nervous system (CNS) prophylaxis. All phases of chemotherapy can suppress the WBC, neutrophils, and platelets.

In this study, all subjects included were in the maintenance phase to standardize the

research. Maintenance therapy is intended to kill any residual cell that was not killed in the remission induction and intensification phases. Daily treatment includes the oral intake of mercaptopurine (40-50mg/m^2) for 6 days in a week; once weekly oral intake of methotrexate (15-20 mg/m^2); once monthly one-day course of intravenous vincristine (1.5mg/m^2 dose); and a 5 day oral prednisone (15-20 mg/m^2 PO) after vincristine given monthly. [7] This regimen is usually given for 36 months.

The bovine colostrum (Pro-Ig) used in this study is a granulated powder produced via thermisation treatment from France. It also contains food additives such as silicon dioxide and dextrose monohydrate. The only contraindication of this product is hypersensitivity to any component of the product. According to Dr. Keech, individuals who are lactose intolerant can easily tolerate up to 12 grams of colostrum per day without any negative side effects or symptoms. The proline-rich polypeptide in colostrum normalizes or modulates the levels of cytokines in the body, so the body does not recognize the lactose as a food allergen in cases of lactose intolerance.[8]

Noted in this study, bovine colostrum use during chemotherapy showed positive effects on the WBC, platelet, and ANC of ALL patients undergoing maintenance chemotherapy. There were no untoward events nor infections noted during the study until 7 days post-intervention. The beneficial effects noted here support the findings of previous studies by Tyrell, Lesmana et.al, Struff et.al, and Jamaroli et.al, that colostrum enhances the effect of immunoglobulins, and decreases signs and symptoms of upper respiratory tract infection, diarrhea, and sepsis. The increase in neutrophils as noted in this study is contrary to the finding of neutropenia on 2 patients given colostrum as reported in a FactMed analysis in 2012. The noted decrease in both hemoglobin and hematocrit may still be due to chemotherapy but the possible causes for significantly lower hematocrit observed in the bovine colostrum needs further investigation.

The decrease in the white blood cells including neutrophils, eosinophils, lymphocytes etc. is the common trend after chemotherapy however in this study, increase in the eosinophils was noted in both treatment groups. Increase in eosinophils is commonly seen among patients with hypersensitivity and parasitic infestations, however, there were no clinical manifestations of these conditions among treatment groups, hence this needs further elucidation.

The beneficial effects of bovine colostrum as seen in this study are promising and potentially beneficial for patients undergoing chemotherapy.

The scarcity of published data on the effects of bovine colostrum on blood parameters especially CBC, ANC and platelet counts made it challenging to conclude that such beneficial effects are directly due to bovine colostrum.

CONCLUSION

This study shows that bovine colostrum is effective in increasing the absolute neutrophil count among ALL patients undergoing maintenance chemotherapy thereby.

RECOMMENDATIONS

This study had small population size hence further studies with adequate sample size is recommended in order to validate the results of this study. Investigations on the effect of bovine colostrum on other forms of cancer is likewise a good endeavor to pursue.

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ORIGINAL ARTICLE

PREDICTIVE FACTORS OF TREATMENT FAILURE FOR PEDIATRIC COMMUNITY-ACQUIRED PNEUMONIA C AND D IN 2-TO-59 MONTHS OF AGE

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ABSTRACT

Objective: To determine antibiotic treatment failure rate and predictors of treatment failure in children 2 to-59 months with Pediatric Community-Acquired Pneumonia-C (PCAP-C) and PCAP-D admitted at Makati Medical Center.

Methods: This prospective cohort study examined 100 children, 2-to-59 months with clinically diagnosed PCAP-C and PCAP-D. Baseline assessment was done on day 1 of hospital stay and follow-up assessments were done on days 3 and 7 or upon discharge for the outcomes of interest.

Results: One hundred children were included in the study and 98% had PCAP-C. This study identified a treatment failure rate of 17% among children with PCAP-C. There was no mortality. Malnutrition and low oxygen saturation on admission were significant predictors of treatment failure.

Conclusion: Antibiotic treatment failure rate was 17%. Malnutrition and hypoxia were significant predictors of treatment failure in children with PCAP-C.

KEYWORDS:

Pediatric Community-Acquired Pneumonia, severe pneumonia, lower respiratory tract infection, malnutrition, hypoxia

INTRODUCTION

Pneumonia is a leading cause of death accounting for 17% of all under-five deaths worldwide, or a loss of roughly 1.6 million lives. Around 90%-95% of these deaths occur in developing countries. According to the United Nations International Children's Emergency Fund (UNICEF), data back in September 2013 showed that majority of deaths occurred in sub-Saharan Africa and South Asia. Data from the Philippines in the same year showed that pneumonia was a top cause of infant mortality with a rate of 1.8/100,000 population; in children, 1-to-4 years mortality rate is 25.2 /100,000 population. [1] This trend was consistently observed over the last five years.

The etiology of pneumonia varies with age. For children less than two, the most common cause are viruses. In school-age children, bacterial pathogens such as *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* are more prevalent, followed by *Haemophilus influenzae* and *Chlamydia pneumoniae*. Other bacterial causes include *Staphylococcus aureus* and *Bordetella pertus*sis.

Treatment outcomes for pneumonia may vary depending on age, vaccination status, immunologic status, exposures, severity of disease, and the setting where the pathogen was acquired.

In a case-control study by Jain, et al involving children 3-to-59 months, most pneumonia deaths were associated with treatment failure.[2] Infancy, lack of measles immunization, severe malnutrition, tachypnea, hypoxemia at baseline, and presence of bacteremia were significant predictors of treatment failure.

A prospective longitudinal survey of children 2-59 months in 2009 by Agweya, *et al*, in Kenya found treatment failure rates ranging from 1.8% to 12.4% for severe pneumonia, and 21.4% to 39.3% for very severe pneumonia.[3] Treatment failure was defined as the development of severe pneumonia or death at any time, and the absence of improvement in the following for severe pneumonia: chest indrawing, measured temperature reduction of $\geq$ to 0.5 C, respiratory rate reduction of $\geq$ to 5 cycles/minute, identification of pathogen with *in vitro* resistance to antibiotics, and a senior clinician's decision to change antibiotic. For very severe pneumonia, treatment failure would mean all the conditions mentioned in severe pneumonia, plus deteriorating level of consciousness, the presence of lung abscess and/or bullae formation, inability to drink, and the requirement for supplementary oxygen on the second and fifth day of treatment. The study found that treatment failure rates varied due to non-adherence to treatment guidelines on pneumonia.

In the Philippines, there is paucity of research on predictors of treatment failure for PCAP-C and PCAP-D among children under five. One local prospective study was done by Lupisan, *et al*, in Bohol in 2007 suggested that for children aged 2-to-5 months, dense infiltrates on chest radiography and presence of bacterial pathogens in the blood would predict death.[4]

This study aimed to identify predictors of treatment failure in children less than five years with Pediatric Community-Acquired Pneumonia-C (PCAP-C) and PCAP-D admitted in a private tertiary hospital.

Specifically, this study determined whether the following factors are predictors of treatment failure: age, gender, immunization status (to *Haemophilus influenzae* type B (Hib) and *Streptococcus pneumoniae*), presence of associated symptoms suggestive such as vomiting or diarrhea suggestive of a viral etiology, exclusive breastfeeding for 6 months, care-seeking delays (more than three days), low

socioeconomic status (income below 30,000 per month) and choice of empiric antibiotic. It also determined whether low oxygen saturation (<92%), malnutrition (z-score of less than -2) and tachypnea are predictive factors of treatment failure.

If predictors for treatment failure are identified, timely changes in management choices to address these predictors for failure may be done. This will translate to a decrease in morbidity/mortality and subsequently improve the treatment outcome of patients with pneumonia.

MATERIALS AND METHODS

This prospective cohort study was conducted between September 1-October 24, 2016 at a private tertiary hospital in the Philippines.

Children, 2-to-59 months old, clinically diagnosed with pneumonia based on the presence of cough and/or dyspnea, or tachypnea for age, and with either wheezing or crackles on physical examination, were included. Patients were classified as PCAP-C if they had the following: respiratory rate ≥60/minute (3-12 months), ≥50/minute (1-5 years), ≥35/minute (above 5 years), intercostal and subcostal retractions, head bobbing, cyanosis, moderate dehydration, moderate malnutrition, and presence of pallor. Children were classified as PCAP-D if they had the following: respiratory rate > 70/minute (3-12 months), >50/minute (1-5 years), > 35/minute (above 5 years), supraclavicular, intercostal, subcostal retractions, grunting, apnea, cyanosis, head bobbing, severe dehydration, severe malnutrition and altered level of sensorium.

Excluded were children with any of the following conditions as these may affect the treatment outcome: on antibiotic therapy for 48 hours before admission, on anti-tuberculous medication, with asthma or any abnormal lung pathology i.e. Bronchopulmonary Dysplasia, Congenital Cystic Adenomatoid Malformation, with immunodeficiency disorder; with congenital heart disease or heart murmur; and with cardiac pathology based on electrocardiography or echocardiography.

Using the Raosoft sample size calculator with a margin of error of 5%, and confidence interval of 95% given the population size of 102 patients with PCAP-C and PCAP-D (from the census of September 1 to October 31, 2015), the minimum recommended sample size for both PCAP-C and PCAP-D was 81.

Treatment failure was defined as failure to improve or have normalization of the respiratory rate (RR + or – 5 cpm), oxygen saturation, (oxygen saturation < 92%), and temperature (temperature > 38), with the presence of pulmonary complications and/or presence of clinical danger signs (severe chest wall indrawing, grunting, inability to breastfeed or drink, lethargy and convulsion, or death within 72 hours from onset of treatment (PCAP Guidelines, Philippine Academy of Pediatric Pulmonologist, 2012).[5]

Baseline data were gathered from the patients' history, physical examination and oxygen saturation at room air were recorded using a portable pulse oximeter.

Methodology

After Institutional Review Board (I.R.B.) approval was secured, the investigator conducted an information session with the medical staff of the Department of Pediatrics of the Medical Center, where the objectives, purpose, and method of the study were discussed.

Informed consent was obtained prior to enrollment.

The pediatric resident on duty recruited and screened the patients in the pediatric

emergency room (E.R.) based on the inclusion criteria. The resident then classified the patients as PCAP-C or PCAP-D. When an overlap between the two categories was seen, the presence of a minimum of two clinical variables sufficed to classify the patient to a higher category (PCAP-D from PCAP-C). The same pediatric resident gathered information regarding patient's history and physical examination and laboratory results. The chest radiograph, if requested, was not used as an inclusion criterion since the diagnosis of pneumonia was based on clinical parameters.

Baseline clinical assessment and laboratory work-ups as ordered by the attending physician were performed at the E.R. prior to the administration of the first dose of antibiotics.

Clinical pneumonia was considered in patients with cough and/or respiratory difficulty, plus any of the following predictors: tachypnea in a patient aged 3 months to 5 years, fever at any age or oxygen saturation less than, or equal, to 92% at room air at any age in the absence of any co-existing illness (neurologic, musculoskeletal, or cardiac condition) that may potentially affect oxygenation (PCAP guidelines, 2012). Bacterial pneumonia was considered when the patient had high-grade fever but without wheezing for children less than 2 years old or for those more than two years old, with the following findings: alveolar consolidation on chest x-ray, and elevated serum C-reactive protein (C.R.P.), procalcitonin and/or elevated white blood cell count. The bedside nurse recorded the vital signs every four hours. Supportive therapy such as oxygen supplementation, antipyretics, and treatment with bronchodilators was given, as needed.

All treatment instituted as ordered by the attending physician was noted, whether they were part of the current treatment guidelines for pneumonia or not. Any changes to the current antibiotic treatment made by the attending physician were also recorded.

All patients who were diagnosed to have clinical pneumonia were followed up in the wards or ICU where the principal investigator measured the outcomes of a 72-hour treatment. The status of the patient was also noted on the seventh day of admission or on the day of discharge, whichever came first.

The subjects' clinical characteristics and socio-demographics were summarized in frequency tables using binary logistic regression analysis to determine predictors of antibiotic treatment failure of PCAP-C and PCAP-D. Predictors with a p-value of less than 0.05 on multivariate regression analysis were considered as significant independent predictors of antibiotic treatment failure.

RESULTS

Out of the 138 children admitted for pneumonia during the study period, 100 fulfilled the inclusion criteria and gave consent for the study. Thirty-eight were excluded due to previous antibiotic treatment for the current illness or ongoing treatment for tuberculosis or with concomitant asthma. Out of the 100 subjects, 98 had PCAP-C and 2 had PCAP-D. Sixty-three percent were male and 85% belonged to the middle class. Fifty-seven percent completed pneumococcal vaccination and 86% completed Hib vaccination. Intravenous cefuroxime was the antibiotic of choice for 70% of the patients.

Eighty-three percent had successful treatment outcomes while 17% were treatment failures. Children in the treatment failure group had a mean age of 19.5 months, while those in the treatment success group had a mean age of 22.7 months. Males predominated in both treatment success (61%) and treatment failure groups (71%). Most patients from the treatment failure group (88%) and the treatment success

group (84%) were from the middle class (88%). Breastfeeding rates for treatment failure group were 29% and 27% for treatment success group. Care-seeking delays were not seen in the treatment failure group (94%) and treatment success group (87%). Symptoms suggestive of viral etiology were seen in the treatment failure group (5%) and treatment success group (13%).

A lower pneumococcal vaccine completion rate was seen in the treatment failure group (29%) than the treatment success group (62%). A lower HiB vaccine completion rate was also seen in the treatment failure group (65%) than the treatment success group (90%). However, the differences in immunization rates between the two groups were not found to be statistically significant Oxygen saturation upon admission for the treatment failure group was 92.5% and 95% for the treatment success group.

Diagnostic procedures requested for both groups included chest radiographs and complete blood counts. Mean white blood count for treatment success and treatment failure groups were 10.5 and 9.7, respectively.

Table 1 shows the antibiotics used upon admission. Cefuroxime was the drug of choice for 70% of patients, followed by azithromycin (24%), and amoxicillin-clavulanate (11%).

Table 1. Antibiotics used for pneumonia) (N=100)

Antibiotics	Frequency	Percentage
Cefuroxime	70	70%
Azithromycin	24	24%
Co-amoxiclav	11	11%
Ampicillin-sulbactam	9	9%
Clarithromycin	9	9%
Amikacin	6	6%
Piperacillin-tazobactam	4	4%
Clindamycin	1	1%
Cefotaxime	1	1%

Table 2 shows that in the treatment success group, the antibiotics most commonly used were cefuroxime (50.6%) and a combination of cefuroxime and azithromycin (21%)

Table 2. Antibiotics used in Treatment Success Group (n=83)

Antibiotics	Frequency	Percentage
Cefuroxime	42	50.6%
Cefuroxime + Azithromycin	17	21%
Co-amoxiclav	5	6%
Piperacillin-tazobactam	3	4%
Ampicillin-sulbactam + Clarithromycin	3	4%
Co-amoxiclav + Clarithromycin	3	4%
Azithromycin	2	4%
Cefuroxime + Amikacin	2	4%
Ampicillin-sulbactam + Azithromycin	2	2%
Piperacillin-tazobactam + Azithromycin	1	1%
Ampicillin-sulbactam	1	1%
Ceftriaxone	1	1%
Co-amoxiclav + Amikacin	1	1%

Table 3 shows that in the treatment failure group, the antibiotics most commonly used were cefuroxime (41%) and a combination of ampicillin-sulbactam and clarithromycin (12%). Table 4 shows that persistence of tachypnea (47%), fever (18%) and chest retractions (18%) were the most common reasons for a change of the initial antibiotic regimen. Table 3 shows in those who did not respond to the first line drugs, treatment modifications made were the addition of a macrolide (47%) OR a shift to piperacillin-tazobactam (30%).

Table 3. Antibiotics used in Treatment Failure Group

First line Antibiotics used	Frequency	Percentage
Cefuroxime	7	41%
Cefuroxime + Amikacin	2	12%
Ampicillin-sulbactam + Clarithromycin	2	12%
Ampicillin-sulbactam	1	6%
Azithromycin	1	6%
Co-amoxiclav	1	6%
Co-amoxiclav + Azithromycin	1	6%
Clarithromycin	1	6%
Cefotaxime + Azithromycin	1	6%
Total	17	100%
Second line Antibiotics used	**Frequency**	**Percentage**
Added Azithromycin	5	30%
Added Clarithromycin	1	6%
Added Ampicillin-sulbactam	1	6%
Ampicillin-sulbactam + Amikacin	1	6%
Amikacin + Clarithromycin	1	6%
Cefuroxime	1	6%
Clindamycin	1	6%
Piperacillin-tazobactam + Azithromycin	1	6%
Vancomycin	1	6%
Piperacillin-tazobactam	4	24%
Total	17	100%

Table 4. Reasons for shifting antibiotics

Persistence of the following:	Frequency	Percentage
Tachypnea	8	47%
Fever	3	18%
Retractions	3	18%
Fever + tachypnea	1	6%
Fever + retractions	1	6%
Tachypnea + retractions	1	6%
Total	17	100%

Predictors of first-line antibiotic treatment failure are summarized in table 5a, 5b, and 5c. Using logistics regression analysis, significant predictors of treatment failure were malnutrition and low oxygen saturation upon admission.

DISCUSSION

This prospective cohort study evaluated the antibiotic treatment success and failure rates among patients 2-to-59 months old admitted to a tertiary hospital for PCAP-C and PCAP-D. The antibiotic treatment failure rate was 17%. Among all the variables studied, only malnutrition and hypoxemia upon admission were found to be significantly associated with treatment failure. Treatment failure was assessed and antibiotic regimen was altered due to continued tachypnea (47%), fever (18%) and chest retractions (18%). Though differences in pneumococcal (63% vs 29%) and Hib (40% vs 65%) vaccinations were seen among the treatment success and treatment failure groups, the differences were not statistically significant. The most common initial regimens used were cefuroxime and a combination of cefuroxime and amikacin. When treatment failure was assessed adjustments in the treatment made were the addition of a macrolide (47%) and a shift to a very broad-spectrum agent, piperacillin-tazobactam (29%). No specific antibiotic was found to be significantly associated with treatment failure.

Malnutrition was the strongest predictor of treatment failure. This is consistent with a case-control study by Jain, *et al*, where cefotaxime for infants and intravenous ampicillin for older children were used, which showed malnutrition to be the strongest predictor of treatment failure.[2] In a two-year longitudinal community-based study in Muntinlupa, Tupasi, *et al,* found that among children less than 5 years old, malnutrition, household crowding, parental smoking, and age less than 2 years were statistically associated with an increase in morbidity due to acute respiratory infection.[6]

Table 5a. Logistic regression analysis of predictors of treatment failure

		Odds Ratio	95% Confidence Interval		P-value
			Lower Bound	Upper Bound	
Age *(Mean, SD)*		0.999	0.947	1.054	0.977
Gender	Female	0.598	0.135	2.647	0.498
	Male	C			
Immunization status (Pneumococcal)	Complete	0.310	0.057	1.700	0.177
	Incomplete	1.666	0.161	17.255	0.669
	None	C			
Immunization status (Hib)	Complete	0.095	0.007	1.222	0.071
	Incomplete	0.280	0.017	4.521	0.370
	None	C			
Presence of other symptoms suggestive of viral etiology	Yes	0.729	0.068	7.841	0.794
	No	C			
Exclusively breastfed (at least 6 months)	Yes	3.763	0.748	18.940	0.108
	No	C			
Presence of care seeking delays (more than 3 days)	No	0.387	0.082	1.827	0.231
	Yes	C			
Socioeconomic status	Middle	5.211	0.489	55.532	0.171
	Upper	C			

Table 5b. Logistic regression analysis of predictors of treatment failure

		95% Confidence Interval		
	Odds ratio	Lower bound	Upper bound	P-value
Oxygen (Mean, SD)	0.836	0.706	0.989	0.037
Respiratory Rate (Mean, SD)	0.468	0.902	1.048	0.973
Malnutrition Yes No	6.253	1.128	34.673	0.036

Table 5c. Logistic regression analysis of predictors of treatment failure

Antibiotics	Odds ratio	P-value	Interpretation
Ceftriaxone	3.39E+09	1.000	Not significant
Piperacillin-tazobactam	2.15E+09	0.999	Not significant
Cefuroxime	20.709	0.065	Not significant
Co-amoxiclav	11.272	0.141	Not significant
Azithromycin	5.772	0.225	Not significant
Ampicillin-sulbactam	4.473	0.356	Not significant
Clarithromycin	1.012	1.000	Not significant
Amikacin	0.772	0.84	Not significant
Cefotaxime	1.98E-08	1.0	Not significant

A local study on fatal childhood pneumonia found that 32% of children, 86% of whom were infants, who died were undernourished. [7] A recent prospective observational study by Christi, *et al,* showed that among severely malnourished children, the range of bacterial pathogens causing pneumonia is different from the usual pathogens; gram-negative bacteria play a more significant role and are associated with higher mortality. [8] Such gram-negative organisms causing severe pneumonia were often resistant to penicillin, ampicillin, and gentamicin. Severely malnourished children were immunocompromised and might fail to show overt clinical signs of pneumonia due to depressed cell-mediated and humoral response.

Hypoxemia at baseline was also a significant predictor of treatment failure. Sudha, *et al*, in Nepal reported that among children 2-to-35 months, hypoxemia (defined as $\leq$ 90% oxygen saturation) upon admission, younger age, and radiographic consolidation were predictors of treatment failure. [9]

Although this study did not determine specific etiologies of pneumonia, hypoxemia is known to be commonly caused by *Streptococcus*

pneumoniae. This organism is widely considered to be the most common cause of community-acquired bacterial pneumonia. In this study, only 62% of the treatment success group and 29% from the treatment failure group completed pneumococcal vaccination. Although the difference was not statistically significant, this may potentially explain the significantly higher pulse oximetry reading in the treatment success group.

In this study, chest radiography had no role in the initial diagnosis of pneumonia. Nevertheless, radiographic findings were noted, and the majority had bronchopneumonia, followed by lobar infiltrates. In a two-year prospective longitudinal study done in Nepal, lobar consolidation was found to be an independent predictor of treatment failure at 48 hours, especially among penicillin recipients. [9]

When the initial regimen was assessed to be failing, the addition of a macrolide in 47% was the most common adjustment in treatment made. A local prospective study involving 82 in-patients, aged less than 5 years with pediatric community-acquired pneumonia, found that 26% of the sampled children had *Mycoplasma pneumonia infection* based on serologic testing. Among the patients who were mycoplasma IgM-positive, 100% were febrile and coughing, 24% were tachypneic, and 24% were hypoxemic upon admission. [10] In an earlier (2000) unpublished local retrospective study involving 58 children aged 1-18 years with community-acquired pneumonia admitted at Cardinal Santos Medical Center, 22% tested positive for mycoplasma IgM serology. [11] In a similar unpublished local retrospective study on 21 children aged 1-18 years with community-acquired pneumonia admitted at Makati Medical Center, 28% had a positive test for mycoplasma IgM serology; 100% of the mycoplasma IgM-positive patients were febrile and coughing.[12] These local data show that 22% to 28% of children with community-acquired pneumonia may have *Mycoplasma pneumoniae* as the pathogen, which justifies the addition of a macrolide when fever and/or tachypnea did not resolve despite initial antibiotic treatment.

Continued fever in 18% of children in the treatment failure group was a reason for a change in antimicrobial regimen. One probable reason for continued fever is if there are co-pathogens, particularly viruses causing the fever. In a prospective longitudinal cohort study involving 1,978 children less than 5 years old in Muntinlupa, it was found that among the 311 children who developed pneumonia, 33% were infected with a virus, respiratory syncytial virus (12.9%), parainfluenza (5.1%) and adenovirus (3.5%) being the most common causes. [6] However, our study cannot definitely identify viruses as a possible cause of the subjects' pneumonia, as no effort was made to identify specific bacterial or viral pathogens.

Our study indicated that no specific antibiotic was found to be significantly associated with treatment failure. According to the 2015 data gathered from the antimicrobial reference laboratory at the Research Institute for Tropical Medicine, 7.6%, 5%, and 0% of *S. pneumonia*e isolates collected from 22 sentinel hospitals nationwide were resistant to penicillin, erythromycin, and ceftriaxone, respectively. For *Haemophilus influenzae*, 8.9%, 3.4%, and 0% were resistant to ampicillin, ampicillin-sulbactam, and azithromycin, respectively. [13] With these relatively low resistance rates of presumed common respiratory bacterial pathogens, all antibiotic treatment given in the study subjects are adequate to treat the bacterial pathogens known to cause pneumonia.

CONCLUSION

The antibiotic treatment failure rate in patients with PCAP-C was 17%. Malnutrition and

hypoxia at baseline were significant predictors of antibiotic treatment failure in children with PCAP-C.

RECOMMENDATIONS

The use of pulse oximeter is a simple, cost-effective way to determine children at risk for treatment failure. This study recommends measurement of oxygen saturation and should always be done in children diagnosed to have pneumonia.

This study also recommends etiologic investigations for pneumonia e.g. viral agents such as influenza and RSV and serologic testing for Mycoplasma to determine the cause of continued fever and tachypnea especially in patients unresponsive to treatment.

LIMITATION

Because there are only two cases of PCAP-D, we are unable to give any significant conclusions about this group.

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Canapi AM, Wong J and Mendoza KI. Effect of a PowerPoint lecture vs video presentation on knowledge and attitude on HIV among Grade 9 public school students

ORIGINAL ARTICLE

EFFECT OF A POWERPOINT LECTURE VS VIDEO PRESENTATION ON THE KNOWLEDGE AND ATTITUDE ON HIV AMONG GRADE 9 PUBLIC SCHOOL STUDENTS

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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: This study aimed to compare the effect of a powerpoint lecture versus video presentation on the knowledge and attitude on HIV among grades 9 students in a public school in Manila.

Methodology: GRADE 9 public school students were randomly assigned into one of two groups, video presentation or PowerPoint presentation. Pre- and post-tests were administered to assess the efficacy of an intervention. Student t-test was used to compare knowledge on HIV/AIDS before and after the intervention, as well as compare the results between the 2 groups. Chi-square was used to compare scores on attitude before and after the intervention, with the level of significance at p=0.05.

Results: Two hundred fourteen students participated in the study, and majority (57%) are females. The mean age of participants is 14.2 years. The difference in scores before and after the intervention was found to be statistically significant ($p<0.001$) with an approximate increase by 16% and 24% after a video and Powerpoint presentation respectively. The difference between post-intervention scores is statistically significant ($p <0.001$; 95% confidence interval) in favor of the PowerPoint presentation.

Conclusions: A PowerPoint lecture is more effective than a video presentation in increasing knowledge and developing positive attitude towards HIV/AIDS.

KEYWORDS:
HIV education, HIV prevention

INTRODUCTION

Adolescents in the 15-24-year age group comprise 29% of newly diagnosed HIV/AIDS cases in the Philippines (1). Data from the HIV/AIDS Registry, 2016 show that the figures have increased by 230% from 2011.In fact, HIV/AIDS is now considered the second most common cause of death among adolescents globally with an estimated 120,000 dying of AIDS-related illnesses.[3]

Adolescents have an increased risk of having sexually transmitted infections, and this may be attributed to the adolescents' early engagement in high risk behaviors. Other reasons which could account for the increase in cases are the lack of knowledge on transmission, such as indiscriminate tattooing and body-piercing.

Due to the increase in HIV/AIDS cases among adolescents, the UNICEF and WHO established the "All in to #End AdolescentAIDS" to accelerate reduction in AIDS-related deaths and infections. By 2020, the program aims to attain zero new HIV infections, zero AIDS-related deaths and zero discrimination. This can be done by maximizing adolescent leadership, mobilization and engagement in social issues, focusing on human rights and equity, and providing sexual and reproductive health education. In the Philippines, the Department of Health (DOH) has launched an HIV/STI prevention program which aims to reduce transmission of HIV and to mitigate its impact at the individual, family and community levels. The program includes strategies and interventions such as peer education and outreach, HIV counseling and testing services and empowerment of communities.

Several studies were done abroad to evaluate the efficacy of an HIV awareness program among school children with positive effects. Awareness and appropriate knowledge play an important role in preventing further the spread of HIV/AIDS among the general population. Understanding the present knowledge and attitude of adolescents can be used to develop and improve existing HIV prevention strategies among Filipino youth. This study aimed to compare the effect of a PowerPoint lecture versus video presentation on the knowledge and attitude on HIV among grades 9 students in a public school in Manila.

METHODOLOGY

Study design: This was a randomized-controlled trial.

Participants: Six sections of Grade 9 students from a public school in Manila were included in the study. Six sections were grouped into 2: Group A - HIV/AIDS awareness video and Group B - didactic lecture.

All participants were asked to answer an HIV knowledge and attitude questionnaire (see Appendix 5), after which cluster randomization was done. Interventions were assigned by use of the random function of Microsoft Excel. The knowledge and attitude scores of the respondents before the intervention served as the control.

Questionnaire: The questionnaire was adopted from the study of Gao *et al* conducted in 2012 in China. The first part focused on the demographic information of respondents. Gender, age, grade level and parents' educational status were included. The second part looked into the knowledge of students on HIV/AIDS as well as their Attitude towards people living with HIV. The questionnaire was validated before the actual conduct of the study.

Intervention: All the students assigned to Group A were gathered in a room. A research assistant introduced the topic and played the video without interruption. It is a 7-minute HIV awareness video

from the Catholic Bishop's Conference Pastoral – National Secretariat for Social Action and the Philippine Catholic HIV and AIDS Network. Authorized permission for its use was obtained prior to the actual presentation. The video included basic information on HIV, its cause and modes of transmission, as well as prevention of the disease. After the video, the respondents' knowledge and attitude on HIV were evaluated using the self-administered questionnaire.

In another room, students who were assigned to Group B were given a didactic lecture using a PowerPoint presentation. A research assistant gave the lecture using an instructional PowerPoint with permission from the Health Promotion and Communication Service Resource Center of the Department of Health. The respondents' knowledge and attitude on HIV were evaluated again using the self-administered questionnaire. Factual contents on HIV are the same for both the PowerPoint lecture and video presentation to avoid bias.

Outcome measures: Quantitative scores (0-100%) on the written examination were obtained and changes in pre- and post-intervention scores were compared between the 2 groups.

Sample size: In this study, comparison of 2 proportions was employed. A study by Gao et al (2012) showed that the proportion of subjects with increased knowledge and positive attitude after an HIV lecture was 89.68% and 83.93%, respectively; a significant difference of 22.34% and 15.23% as compared to p_0 intervention is acceptable.

The formula was

$$n = \frac{(Z_{\frac{a}{2}} + Z_b)^2 \; x \; [p1(1-p1) + p2\,(1-p2)]}{(p1-p2)^2}$$

Where

n = sample size required in each group

$p1$ = proportion of subjects with correct knowledge or positive attitude after the lecture

$p2$ = proportion of subjects with correct knowledge or positive attitude before the lecture

$p1 - p2$ = clinically significant difference

At 5% level of significance, power of 80%, using two-tailed z-test of proportion, the highest computed sample size was 104.

Data analysis:

IBM® SPSS Statistics version 24 software was used in the data analysis. Baseline data were analyzed using descriptive statistics. Normality of HIV scores was assessed using the Kolomogorov-Smirnov test. Student t-test was used to compare HIV/AIDS knowledge awareness and attitude before and after the intervention, and compare the scores between the 2 groups. Chi-square was used to compare the HIV attitude scores before and after the intervention. Significance level was set at 0.05.

Ethical considerations: Ethics approval was obtained prior to the conduct of the study. Permission was also obtained from the regional office of the Department of Education as well as the school principal. A written informed consent and assent were obtained from all parents and students prior to data collection. Participants were free to decline from answering questions that made them feel uncomfortable.

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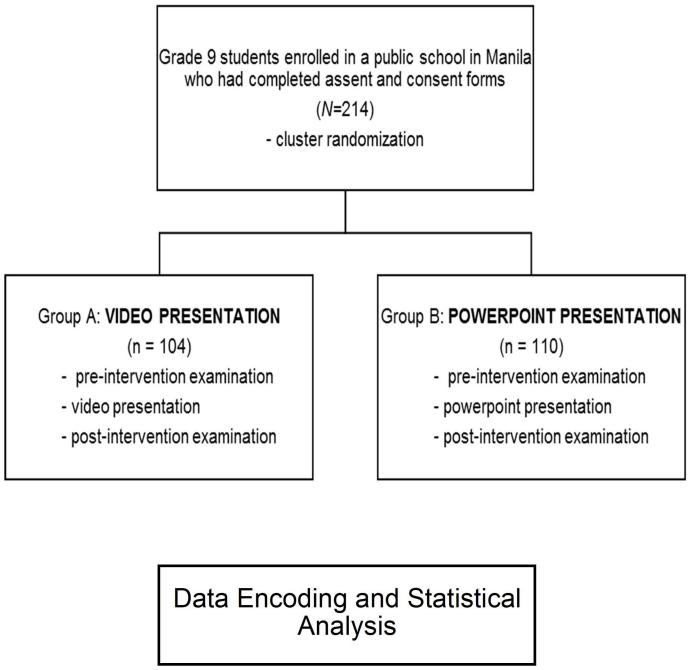
Figure 1. Flow Chart of the Methodology of the Study



RESULTS

Study Population

Two hundred fourteen (214) students participated in the study, 123 of whom (57%) are females. The mean age is 14.27 years. Parents of participants finished college (49.5%) and high school (48.6%) respectively.

Knowledge Sources of HIV/AIDS

Most obtained information on HIV/AIDS through television (87.4%), followed by newspaper (14.4%), and through family (14%), with the school as the least source of information on HIV/AIDS (1.4%).

HIV/AIDS Knowledge Situation before and after Intervention

In the video group pre-intervention (see table 3), more than 75% knew that AIDS is caused by a virus, that it is an infectious disease, and that it can be prevented. Majority (95%) identified unprotected sex as a mode of transmission of HIV/AIDS. However less than a quarter (<75%) believed that shaving/tattooing/ear piercing using unsterilized tools and breastfeeding can transmit the disease.

Table 1. Socio-demographic characteristics of study participants

	N = 214	%
Gender		
Males	91	42.5
Females	123	57.5
Age (years)		
13	12	5.6
14	130	60.7
15	59	27.6
16	12	5.6
Father's Education		
Elementary	11	5.2
Graduate	97	45.3
High School	106	49.5
graduate		
College Graduate		
Mother's Education		
Elementary	10	4.7
Graduate	104	48.6
High School	100	46.7
graduate		
College Graduate		

Table 2. Source of Information on HIV/AIDS

	N = 214	%
Television	187	87.4
Friend	25	11.7
Newspaper	31	14.4
Family	30	14.0
Radio	21	9.8
School	3	1.4

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Table 3. Percentage and comparison of HIV/AIDS knowledge before and after intervention

	Video					PowerPoint				
	Before		**After**		P-value	**Before**		**After**		P-value
	N	%	N	%		N	%	N	%	
Basic Medical Knowledge										
Is AIDS caused by a virus	81	78.64	96	91.43	0.002	85	77.27	103	93.64	0.005
A person can be known infected from its appearance	56	54.37	70	66.67	0.069	77	70.00	106	96.36	0.001
AIDS is an infectious disease	88	85.44	95	90.48	0.0001	104	94.55	102	92.73	0.580
AIDS can be cured	53	51.46	69	65.71	0.036	84	76.36	106	96.36	0.000
AIDS can be prevented	96	93.20	99	94.29	0.009	106	96.36	108	98.18	0.443
Transmission Knowledge										
AIDS can be transmitted through										
Blood transfusion	76	73.79	99	94.29	**0.046**	104	94.55	110	100.0	0.291
Sharing needle with an infected person	85	82.52	98	93.33	**0.023**	103	93.64	110	100.0	**0.014**
Shaving/tattooing/getting ear pierce with unsterilized tools	64	62.14	72	68.57	**0.000**	83	75.45	86	78.18	0.631
An infected pregnant to her unborn person	88	85.44	102	97.14	**0.034**	104	94.55	106	96.36	0.517
Having unprotected sex with an infected person	98	95.15	104	99.05	**0.000**	104	94.55	110	100.0	**0.029**
Breastfeeding	60	58.25	97	92.38	**0.034**	75	68.18	98	89.09	**0.000**
AIDS cannot be transmitted through										
Hugging/kissing/shaking hands with an infected person	40	38.83	89	84.76	0.0001	49	44.55	102	92.73	**<.05**
Sharing toilet seats/swimming pool with an infected person	51	49.51	100	95.24	0.004	64	58.18	106	96.36	**<.05**
Sharing cups/dinner set/bedding/tools with an infected person	51	49.51	93	88.57	0.0002	52	47.27	98	89.09	**<.05**
Mosquito bites	51	49.51	73	69.52	0.005	71	64.55	105	95.45	**0.000**
Studying in the same classroom with an infected person	36	34.95	82	78.10	0.036	61	55.45	108	98.18	**<.05**
Coughing	53	51.46	91	86.67	0.0004	68	61.82	106	96.36	**<.05**

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For the Powerpoint group, more than 75% of the subjects answered the items correctly except for breastfeeding as a mode of transmission of the disease.

Almost half of participants believed that HIV/AIDS can be transmitted through casual contact with people with HIV/AIDS, by sharing utensils or sharing swimming pools and through mosquito bites.

Post-intervention, both groups had a statistically significant increase in scores.

Figure 2 shows the pre- and post-intervention scores of each group with mean pre-intervention scores of 68% and 70% for the video and PowerPoint groups, respectively.

Table 4 shows that there was no significant difference in the pre-intervention scores between the groups (p=0.128). The mean scores after the intervention were 85% and 94% respectively, with a difference of 9% favoring the PowerPoint presentation.

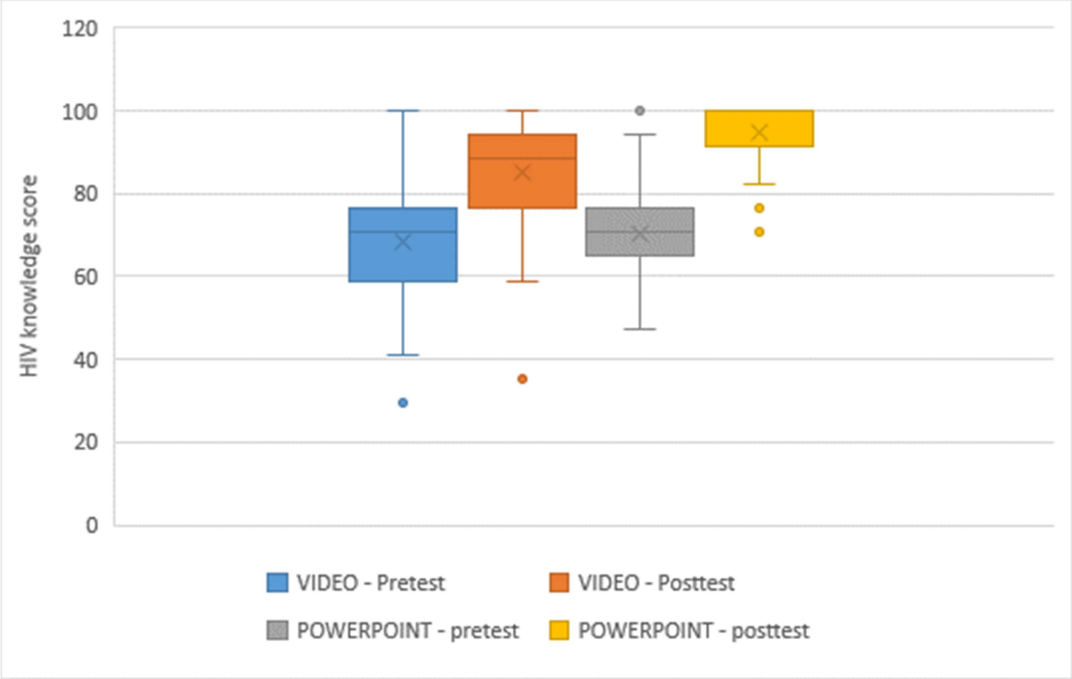

Figure 2. Box plot of HIV knowledge scores grouped per intervention
The x represents the median and the boxes represent the range of scores. Dots represent outlying scores.

The difference in scores before and after the video presentation was statistically significant ($p < 0.001$) with an approximate increase by 16% after the intervention. A similar finding was seen in the PowerPoint group ($p < 0.001$) with an increase by 24%. Comparing the 2 interventions, the difference in post-intervention scores was statistically significant ($p < 0.001$; 95% confidence interval) favoring the PowerPoint group.

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Table 4. Comparison of HIV/AIDS knowledge scores before and after intervention.

	Mean Diff	Std. deviation	Std. error mean	95% confidence interval of the difference		T	df	Sig. (2-tailed)
				Lower	Upper			
Video pretest – Powerpoint pretest	-2.74348	18.65510	1.78683	-6.28529	.79834	-1.535	108	.128
Video pretest – posttest	-16.61893	17.33307	1.66788	-19.92530	-13.31256	-9.964	107	**.000**
Powerpoint pretest – posttest	-24.19245	13.37878	1.25857	-26.68614	-21.69875	-19.222	112	**.000**
Video posttest – Powerpoint posttest	-9.25926	12.14886	1.16902	-11.57671	-6.94180	-7.920	107	**.000**

Attitude towards People Living with HIV/AIDS

Table 5 shows that even before the intervention, majority of participants (91% in the video group and 94% in the video group) said that they would like to help people living with HIV/AIDS. This further increased to 99% and 96% respectively after the intervention. Most of the students (92% in the video group and 94% % in the PowerPoint group) would like to take care of their classmates/families if they were infected with HIV. After the intervention, the rate increased up to 99% and 96%, respectively.

Majority of students believed that HIV/AIDS should be included in the curriculum. As for participation in HIV/AIDS awareness programs, 86 students (83.5%) in the video group and 99 students (90%) in the PowerPoint group wanted to be involved in such activities. This increased to 96.2% and 93.6% respectively, after the intervention. Both interventions had statistically significant changes on attitude towards people living with HIV.

DISCUSSION

This study showed that majority of students obtained information on HIV/AIDS from the media (television and newspaper), similar to the study done in Kosovo (2). This is also consistent with findings of the Young Adult Fertility and Sexuality Survey 2013 (YAFS) where mass media played a significant role on HIV awareness. Although the study by Tan *et al* showed that mass media tended to have negative effects on HIV education due to propagation of misconceptions on the disease, media remains to be an important source of information on HIV (3). It is thus important to monitor how HIV is being portrayed in these sources to ensure that HIV education programs address serious emerging misconceptions about the disease.

In the Philippines, a study by Gao *et al* showed that a minority obtained information on HIV/AIDS through school and from friends and relatives, as parents are thought to have difficulty in speaking openly about the disease (4). In contrast, several

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Table 5. Percentage and comparison of HIV/AIDS knowledge before and after intervention

	Video					PowerPoint					
	Before		**After**		P-value	**Before**		**After**		P-value	
	N	%	N	%		N	%	N	%		
HIV											
Would you like to help a person with HIV/AIDS	94	91.26	103	98.10	**0.0004**	104	94.55	105	95.45	0.096	0.446
Would you like to take care of your family or classmate with HIV/AIDS	95	92.23	104	99.05	**0.002**	104	94.55	106	96.36	0.517	0.369
School should include HIV/AIDS in their curriculum	89	86.41	97	92.38	**0.007**	101	91.82	100	90.91	0.809	0.696
Would you like to participate in HIV/AIDS health information campaign	86	83.50	101	96.19	**0.005**	99	90.00	103	93.64	0.325	0.395

Students relied on the health department through physicians as a source of information on HIV/AIDS. These were likewise noted in this study with the family (14%), and the school as the least source of information on HIV/AIDS (1.4%).

Even before the intervention, students were aware of the causes, transmission, and prevention of HIV/AIDS but some misconceptions were noted. Most knew that HIV/AIDS can be transmitted through unprotected sex, blood transfusion/sharing needles with an infected person and having more than one sexual partner. Although not representative of the youth population, the baseline scores obtained of 68% and 70% for the video and PowerPoint groups respectively were similar with findings from YAFS 2013 where a low percentage of Filipino youth was found to have comprehensive knowledge on AIDS. A significant number of students believed that it can be transmitted by sharing utensils, food and toilet seats with an HIV-infected person, or through mosquito bites. The said results were similar with the findings from YAFS 2013.

These findings also echo the results of Gao where majority of secondary school students knew that AIDS is infectious, and can be transmitted through unprotected sex, blood

transfusion/sharing needles with an infected person, and having more than one sexual partner but can be prevented (4).

There is a small percentage of respondents who believed that it can be transmitted by sharing utensils, food, through fomites such as toilet seats, or through mosquito bites. As to treatment of HIV/AIDS, only a small number of students knew that there is no cure for HIV/AIDS (4).

Different strategies are used in HIV/AIDS awareness programs in schools. Borgia *et al* (2005) showed that peer-led interventions caused an improvement on knowledge of HIV, but teachers still play an important role on HIV awareness among high school students.[11] Majority believed that schools must improve their curriculum about HIV/AIDS (5). In this study, majority of students believed that HIV/AIDS should be included in the curriculum.

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Both interventions had a statistically significant increase in pre- and post-intervention scores on HIV knowledge among the students, with the PowerPoint presentation producing a greater increase. This is in contrast with those of Calderon *et al* where an educational HIV/AIDS video was found to be more effective in conveying knowledge on HIV among high-risk groups (6). These were also contrary to the findings of Schreiber *et al.* (2010) which showed no significant difference between pre- and post-intervention scores after giving live lectures and video presentations (7). Our study showed that although more convenient as a teaching tool, the subjects found video presentations to be less engaging and were less likely to be finished.

Students relied on the health department through physicians as a source of information on HIV/AIDS. These were likewise noted in this study with the family (14%), and the school as the least source of information on HIV/AIDS (1.4%).

CONCLUSION

A PowerPoint lecture was more effective than a video presentation in increasing the knowledge and promoting a positive attitude towards HIV/AIDS among grade 9 public school students in Manila.

RECOMMENDATION

A 6-month follow-up study is suggested to evaluate long-term changes on the knowledge of participants. Prevalence of high-risk behaviors must be included as a measure of efficacy of the intervention.

A larger sample size to include all secondary school students, and even out-of-school youth is also suggested in future studies.

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ORIGINAL ARTICLE

FEVER OF UNKNOWN ORIGIN IN CHILDREN: A FIVE-YEAR REVIEW

ABSTRACT

Objectives: The clinical presentation, outcome, and risk factors for mortality in children with Fever of Unknown Origin (FUO) were determined.

Methods: Medical records of pediatric patients admitted for FUO from January 2009 to December 2013 were reviewed. Clinical manifestations, physical exam findings, diagnostic work-ups and final diagnosis were determined, as well as the relationship between final diagnosis and risk for mortality.

Results: Fifty-seven patients with FUO were included. Weight loss, cough, colds, and rashes were common symptoms while pallor, lymphadenopathies, and hepatomegaly were common physical exam findings. All patients underwent Phase I evaluation for FUO, while 73.7% underwent further diagnostic tests. A specific etiology was established in 96.5% of cases: infectious, 43.9%, connective tissue disease, 38.6%, and hematologic/oncologic, 14%. Two cases remained to have no specific diagnosis. Majority of patients had a benign course and were discharged improved (84.2%). The mortality rate is 15.8% and was not associated with any disease category (p-value 0.204).

Conclusions: FUO in children occurs across all age groups. Its clinical presentations are varied and non-specific and common signs and symptoms are pallor, lymphadenopathies, weight loss, cough, colds. and joints pains. Infection is the most common cause of FUO in children, followed by connective tissue diseases and hematologic and oncologic diseases. The mortality rate from FUO is 15.8%.

KEYWORDS:
Fever of unknown origin, FUO,

INTRODUCTION

Fever is a common constitutional symptom due to a wide array of health conditions. The occurrence of fever in children poses a challenge to pediatricians in daily clinical practice.[1] A prolonged and persistent course with undetermined etiology adds further to the dilemma.[2]

Fever of unknown origin (FUO) is defined as a temperature greater than 38°C documented by a health care provider for which the cause is unidentified after three weeks of outpatient evaluation or after one week of hospital admission.[1] Despite current advances in medicine, there is still no universally acceptable guideline on diagnosis and management of FUO as far as the extent of evaluation, indications for hospital admission, and use of empiric antibiotics are concerned.[2] The Philippine Pediatric Society in 2004 presented phases of diagnostic testing as a guide in evaluating children with FUO. Phase I includes tests such as complete blood count (CBC), erythrocyte sedimentation rate (ESR), urinalysis, Tuberculin skin test (TST), chest x-ray, blood culture and ASO titer. Phase II includes lumbar puncture, repeat blood culture, sinus and mastoid x-rays, serologic tests such as those for Human Immunodeficiency Virus (HIV), Salmonellosis, Brucellosis, Tularemia, Epstein Barr Virus, Cytomegalovirus, Toxoplasmosis, Hepatitis, Fungal infection, and Malaria smear, and liver function tests such as, aspartate transaminase (AST), and alanine transaminase (ALT). Phase III includes abdominal ultrasound, abdominal CT scan, upper GI series, bone marrow aspiration and bone scanning.[3]

At present, there is limited local data on FUO in children. This study aims to determine the presentation, outcome and risk factors for mortality of pediatric patients with FUO admitted under the Department of Pediatrics of the Philippine General Hospital, a tertiary government hospital, from January 2009 to December 2013.

METHODS

This is a retrospective study where data was obtained through review of patient medical records.

Patients 0-18 years old admitted for FUO at the pediatric emergency room, pay and charity wards of the Philippine General Hospital from January 2009 to December 2013 were included.

Patients with known acquired or congenital immunodeficiencies and those FUO patients with incomplete data on the medical records were excluded.

Admission registry logbooks at the Pediatric Emergency Room were reviewed. All patients seen from January 2009 to December 2013 with a chief complaint of prolonged and/or persistent fever documented by a health care provider with unidentifiable cause after 3 weeks of outpatient evaluation and those from other hospitals admitted for more than 1 week for which the cause of fever is still unknown were included. Medical charts of patients who fulfilled the criteria for FUO were retrieved and reviewed for completeness. Complete charts are those with the following information: case number, date of admission, name, age, sex, onset of fever, fever pattern, accompanying signs and symptoms, documented diagnostic evaluation and results, medications, procedures done and final diagnosis. Incomplete charts were excluded.

Specific clinical outcomes (discharged improved, not improved, died) were recorded. Additional data of discharged patients seen on follow-up were also noted based on their outpatient medical records.

Descriptive statistics were used to summarize the data presented as frequencies and proportions or percentages. To analyze the association

between the final etiologic diagnosis for FUO (infectious versus non-infectious causes) and mortality, odds ratios were determined and a p-value of <0.05 was considered statistically significant.

RESULTS

One hundred two cases with an admitting impression of FUO, prolonged fever or persistent fever were identified from the pediatric ER triage logbook. Of these, 59 charts were retrieved from the medical records section. Two charts were incomplete and were excluded. Fifty-seven charts were included in the final analysis.

Table 1 shows the age and sex distribution of patients admitted for FUO. The majority were below 10 years old, with the highest number of cases in the 6 to 9 years old age group. There was a slight female predominance with a ratio of 1.2:1.

Table 1. Age and sex distribution of patients with FUO.

Age (in years)	Male		Female		Total	%
	Number	%	Number	%		
0-2	7	12.3	3	5.3	10	17.5
3-5	5	8.8	6	10.5	11	19.3
6-9	7	12.3	8	14.0	15	26.4
10-14	4	7.0	7	12.3	11	19.3
15-18	3	5.3	7	12.3	10	17.5
Total	26	45.6	31	54.4	57	100

The duration of fever before ER admission ranged from 14 to 281 days with a mean duration of 64 days). The highest temperature recorded was 41°C (mean 39.45°C ±0.64). Most patients presented with intermittent fever (61.4%). Accompanying signs and symptoms varied but the most common symptoms were weight loss (71.9%), cough and colds (52.6%), and joint pains or arthralgia (40.3%). Most common signs were pallor (50.9%), lymphadenopathies (24.6%) and hepatomegaly (10.5%). (Table 2)

SYMPTOMS	Number of Patients (n=57)	Percentage
SYMPTOMS		
Weight loss	41	71.9%
Cough/colds	30	52.6%
Arthralgia	23	40.3%
Rashes	22	38.6%
Abdominal pain	21	36.8%
Anorexia	18	31.6%
Body malaise	18	31.6%
Vomiting	15	26.3%
Headache	14	24.6%
SIGNS		
Pallor	29	50.9%
Lymphadenopathies	14	24.6%
Hepatomegaly	6	10.5%
Bleeding	4	7.0%

Table 2. Signs and symptoms of FUO in

Of the 57 cases, 26.3% had a definite diagnosis after Phase I evaluation, 24.6% needed to undergo Phase II tests, but most cases (49.1%) required Phase III evaluation before a definite diagnosis could be made. Among the 28 who underwent Phase III evaluation, two patients (3.5%) still had no diagnosis until the time of discharge.

Initial laboratory findings of FUO patients are shown in Table 3. More than 50% of cases showed normal white blood cell (WBC) counts, while 38.6% presented with leukocytosis. Urinalysis was normal in the majority, as with chest radiographs in 42.1% of cases. Of the 21 patients where a tuberculin skin test (TST) was performed 7 had a reading of ≥10mm in duration and had TB as a diagnosis. Three patients where the TST reading was <10 mm turned out to be TB cases after additional work-ups.

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Table 3. Laboratory Findings in Patients with FUO.

Parameter	Number of Cases	Percentage
White Blood Cell (WBC) count (n=*57*)		
5000 to 10,000 x10^{9}g/L	30	52.6%
>10,000 x10^9/L	22	38.5%
<5000 x10^9/L	5	8.7%
Urinalysis (n=*53*)		
WBC <10/hpf	30	56.6%
WBC ≥10/hpf	23	43.3%
ESR (n=23)		
≥ 20 mm/hr	8	34.7%
< 20 mm/hr	15	65.2%
CRP (*n= 21*)		
<6 units	7	33.3%
≥6 units	14	66.6%
Chest x-ray (*n= 50*)		
Normal	28	56%
pneumonia	12	24%
hilar lymphadenopathies	8	16%
pleural effusion	2	4%
TST reading (*n=21*)		
≥10mm	7	33.3%
<10mm	12	57.1.0%
unknown	2	9.5%

Table 4 lists the final diagnosis following in-patient diagnostic evaluation. The final diagnoses of most of pediatric FUO cases were infectious in etiology (43.9%) with TB (19.3%), and typhoid fever (10.4%) as the leading causes. Twenty cases were diagnosed to have connective tissue diseases (38.6%), and the majority were identified to have Systemic Lupus Erythematosus (SLE), (17.5%) or Juvenile Idiopathic Arthritis (JIA), (14%). Eight cases (14%) were due to hematologic or oncologic causes, of which acute lymphoblastic leukemia was the most common (10.4%). Two cases (3.5%) remained undiagnosed despite Phase III diagnostic evaluation. In both cases, tuberculosis vs malignancy was considered.

Table 4. Final Diagnosis of Patients with FUO.

Final Diagnosis	Number of Cases	Percentage
I. INFECTIOUS DISEASES	**25**	**43.9**
Tuberculosis	11	19.3
Typhoid Fever	6	10.4
Deep-seated abscess	3	5.3
Complicated pneumonia	2	3.5
Cryptococcal meningitis	1	1.8
Bacterial meningitis	1	1.8
Chronic Pyelonephritis	1	1.8
II. MALIGNANCY	**8**	**14.0**
Acute Lymphoblastic Leukemia	6	10.4
Acute Myelogenous Leukemia	1	1.8
Basal Cell Carcinoma	1	1.8
III. CONNECTIVE TISSUE DISEASES	**22**	**38.6**
Systemic Lupus Erythematosus (SLE)	10	17.5
Juvenile Idiopathic Arthritis (JIA)	8	14.0
Rheumatic Fever	2	3.5
Henoch Schonlein Purpura	2	3.5
Polyarteritis Nodosa	1	1.8
IV. UNDETERMINED	**2**	**3.5**

The duration of hospital stay was shortest in those diagnosed to have an infectious disease as the etiology for the fever, ranging from 5 to 47 days (mean 10.7 ± 8.11 days). Oncologic cases stayed longer, from 11 to 45 days (mean 18.1 ±13.2 days), while those with connective tissue diseases stayed from 6 to 53 days (mean 12.5 ±10.9 days). The 2 cases which remained undiagnosed had the longest hospital stay, 22 and 46 days respectively (mean 34 ±31.1 days).

The outcome of the 57 patients with FUO was generally good, despite the occurrence of 9 deaths (15.8%). The highest mortality was seen in those

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with connective tissue diseases, all of whom were diagnosed to have SLE. Of those with infection as the cause, 23 (92%) were discharged improved with only 2 (8%) mortalities due to sepsis.

Table 5 shows that none of the following risk factors: age, sex, duration of fever before admission, maximum temperature, and presenting symptoms, was a significant predictor of mortality with all the p-values exceeding the level of significance of 0.05

Table 6 shows that the probability of dying from FUO due to a connective tissue disease was 2.5 times greater compared to the other disease categories. However, this was not statistically significant (p= 0.441). The overall p-value of 0.204 signifies that the risk of mortality is not associated with any of the three disease categories.

Table 5. Risk Factors for Mortality among FUO Patients.

Possible Risk Factors	Coefficient	Odds Ratio	p-value
Demographic data			
Gender	1.946	7.000	0.078
Age	-0.572	0.564	0.326
Duration of fever prior to admission	0.038	1.039	0.475
Maximum temperature	-0.016	0.984	0.886
Symptoms			
Weight Loss	-	-	0.998
Headache	-0.900	0.407	0.420
Abdominal Pain	-0.188	0.829	0.811
Vomiting	-0.154	0.857	0.860
Rashes	1.265	3.542	0.110
Watery Stools	0.717	2.048	0.432
Joint pains	0.243	1.275	0.759
Generalized Weakness	0.152	1.165	0.847

Table 6. Relationship between disease category and mortality.

	Coefficient	Odds Ratio	p-value
Disease Category			**0.204**
Infectious Disease	-0.657	0.519	0.612
Connective Tissue Disease	0.916	2.500	0.441
Malignancy	-0.946	0.430	0.069

DISCUSSION

Majority of children with FUO seek consult for generalized systemic complaints which makes diagnosis difficult. Uncommon presentations of common diseases were observed in related FUO studies. Constitutional signs and symptoms including fever may persist independently for weeks or months. Therefore, a thorough and organized approach to diagnose cases of prolonged fever is of great importance. Patience, persistence, repeated history taking, physical examination and continued monitoring offer the best chance of making a diagnosis in difficult cases.[4]

The American College of Emergency Physicians recommends that the initial diagnostic tests for FUO should include only CBC, urinalysis, blood culture, and tuberculin skin testing.[5] However, a study done by Simon and colleagues showed that more than 50% of physicians in the United States emergency departments ordered for rapid microbial testing and radiographs for patients presenting in the emergency room.[6] This practice is attributed to changes in the epidemiology and severity of bacterial infections as a result of widespread vaccination, as well as changes in physicians' clinical judgment over time.[5]

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The extent of laboratory investigation is dependent on the clinical history, physical examination, age of the patient and duration of fever. A complete blood count, urinalysis and chest x-ray are usually performed as part of the outpatient work-up prior to admission.[7]

Laboratory findings such as elevated leukocyte counts suggest an infectious etiology in patients with FUO.[8] However, in this study, majority of patients had normal leukocyte counts even in those with infection as the cause for the fever. Levels of erythrocyte sedimentation rate (ESR) brought by an increase in hepatic synthesis of fibrinogen, as well as other acute phase reactants such as C-reactive protein (CRP), are of no specific value for they are general indicators of an inflammatory process.[9] In this study, 32% to 37% of patients had elevated ESR and an abnormal CRP which necessitated further investigation. Radiographic examination of the chest was routinely done on all FUO patients as part of the initial workup. Majority of patients in this study had normal chest x-rays and only a few were diagnosed to have complicated pneumonia presenting as lobar consolidation, bronchiectasis or pleural effusion. Tuberculin skin testing (TST) is recommended as an initial test among patients with FUO. Guidelines set by the WHO on the interpretation of the TST stated that a positive TST has an induration of greater than or equal to 10mm in all children whether they have received BCG vaccination or not, as well as an induration of greater than or equal to 5mm in immunocompromised individuals (such as HIV-infected children and those who are severely malnourished).[10] In this study, only 7 out of 11 diagnosed TB cases turned out to be TST positive. Three cases with negative tests were eventually diagnosed to have TB after additional invasive procedures (pleural fluid TB culture, bone biopsy, and liver biopsy).

In this study, infectious diseases were the most common causes of FUO, seen in 25 cases (43.9%), with tuberculosis and typhoid fever as the most frequent infectious etiologies. This supports local and foreign studies on FUO[11,12,13,14,15,16] Infections, therefore, should be considered first because of its frequency and therapeutic implications. Connective tissue diseases, mainly SLE and JIA ranked as the 2nd most common causes, seen in 22 patients (38.6%). This is also noted in other studies on FUO conducted abroad.[15,17] Locally, several descriptive studies in different tertiary hospitals showed that the primary etiology of FUO is infection.[8,11,12] Other causes identified were malignancy, connective tissue disorders or no identifiable etiology, similar to those reported in other studies abroad.[9,13,14,15,16] Although there was a high incidence of infection as the cause for FUO in children, the type of infection differed in developed countries compared those in less developed or developing countries.[7,14,17,18] In a systematic review by Chow and colleagues of 18 published studies on FUO across all countries, they reported that the most common infections were typhoid fever, tuberculosis, and brucellosis in developing countries, while osteomyelitis, bartonellosis, and tuberculosis were the most common in developed countries.[15]

Malignancy as the cause of FUO was determined in 14% of cases and the most identified cases were acute leukemia. Just like infections, malignancy has the ability to produce endogenous pyrogens, such as tumor necrosis factor, which is capable of inducing fever both by acting directly on the thalamus and by stimulating other endogenous pyrogens. In patients with neoplastic disease, the tumor necrosis factor is synthesized and secreted continuously by malignant cells.[1]

In the case review of Lohr and Hendly, neither the pattern of fever nor its duration was useful in establishing a diagnosis in children with

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FUO.[9] Most children in this study presented with intermittent fever, however, no particular fever pattern was specific for any of the disease categories. Aside from prolonged fever, accompanying signs and symptoms of patients were generally non-specific, and none were predominantly seen in a specific disease category.

Patients with infection had the shortest duration of hospital stay, with a mean of 10.7 days. These were also the patients who were diagnosed early. On the other hand, the performance of more extensive laboratory work-ups required in the diagnosis of connective tissue and neoplastic diseases have in a way contributed to the prolonged hospital stay of the other patients. Some tests also needed to be sent out to other hospital facilities due to unavailability of such in the hospital laboratory. These tests included ANA, anti-dsDNA, and bone marrow aspiration and biopsy studies.

Tezer and co-authors pointed out in their study that inappropriate use of antimicrobials is a major cause of diagnostic delay.[16] Prior antimicrobial use inhibits the isolation and growth of microorganisms in cultures and prevents seroconversion in diseases such as enteric fever and salmonellosis.[15] In this study, most of the patients were prescribed with various medications from previous consults. Seventy-eight percent had a history of at least 2 antimicrobial courses prior to transfer to our institution. Persistence of fever despite compliance to treatment was the primary reason for transfer for multispecialty/tertiary care. This implies that indiscriminate use of antibiotics for FUO offers no diagnostic or therapeutic benefit and may further obscure the diagnosis.[11] However there are situations where it may be prudent to start empiric antibiotic therapy pending results of diagnostic tests, such as in cases where infection is the primary consideration. Failure to start early and appropriate antibiotic treatment could lead to fatal results.[7] Hence, when a serious infectious disease is suspected, timely investigation, including collection of appropriate specimens for microbiological tests should be conducted prior to empiric antibiotic therapy. Judicious use of antibiotics should be based on the clinical history, physical findings, local epidemiology of disease and suspected etiologic agent.[7]

Children with FUO have a better prognosis since they are less likely to have malignancies or autoimmune processes as the causes of prolonged fever.[7] In this study, FUO patients generally had a benign course and improvement was seen after treatment in 96.5% of cases. In two cases, FUO was suspected to be either due to malignancy or tuberculosis but remained undetermined despite thorough investigation. Both remained stable and were sent home after they were afebrile for more than 48 hours, and even prior to the release of the liver and bone marrow biopsy results. Further diagnostic work up was planned in the outpatient clinic but was not done because they were eventually lost to follow-up. In the study of Velarde, 8% of cases remained undiagnosed but were discharged afebrile and stable.[11] In foreign studies, 10-20% of cases remained undiagnosed despite prolonged work up.[6,16]

Mortality rate was reported at 15.8% in this study and was not associated with any of the disease categories (p-value 0.204). Although the risk of dying was 2.5 times greater in those diagnosed to have a connective tissue disease with 6 of 9 deaths (66.7%), this was not shown to be statistically significant, but could probably be due to the small sample size. Age, gender and presenting signs and symptoms were not shown to predict adverse outcomes.

In a study done among adult FUO patients in 2014, the mortality rate was reported at 6.9%, of which 60% were due to malignancy, specifically Non-Hodgkin's lymphoma. All 164 patients whose

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diagnosis remained undetermined at the time of discharge survived. Factors associated with mortality were diagnosis of malignancy, age, continuous (as opposed to episodic) fever, anemia, leucopenia, LDH levels, and hepatomegaly.[19]

Limitations of this study include a considerable number of missing charts, with a retrieval rate of only 57.8%. Other problems encountered were missing results of diagnostic tests done during admission such as x-rays, urinalysis, CRP, ESR, ultrasound, and biopsy, which may have affected the findings in relation to the variables evaluated in the study.

Although a larger sample size might generate different results as to the true number of cases in each of the disease categories as well as the definite diagnosis, this study showed comparable results with similarly conducted studies.

CONCLUSION

Fever of unknown origin in children occurs across all age groups, with the majority of cases occurring in those 6-9 years of age. Clinical presentations are varied and non-specific. The most common symptoms were weight loss, cough and colds, and joint pains, while most common signs were pallor, lymphadenopathies, and hepatomegaly. The most common cause of FUO in children is infection with TB as the most common cause. This is followed by connective tissue diseases and hematologic or oncologic conditions. Mortality rate was 15.8% with the majority of deaths attributed to connective tissue diseases. None of the disease categories were found to be significantly associated with mortality.

RECOMMENDATION

Although this study reflects the findings of other studies done locally and abroad, a multicenter prospective study to determine the clinical profile and outcome of pediatric FUO cases in the Philippines will be more helpful in generating statistically significant outcomes and robust conclusions. Results of larger studies will also help in formulating concise diagnostic and management guidelines for FUO in children.

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CASE REPORT

CHRONIC GRANULOMATOUS DISEASE: AN UNREPORTED MUTATION

ABSTRACT

Chronic Granulomatous Disease (CGD) is caused by defects in the phagocyte NADPH oxidase and occurs in approximately 1:200,000 births worldwide. It presents with early onset of severe recurrent bacterial and fungal infections. This is a case of a 9-year old male with severe, recurrent bacterial infections since 3 weeks of age. Initial Nitroblue tetrazolium (NBT) reduction tests were normal but a DNA analysis revealed a previously unreported homozygous mutation in *CYBB*, p.S418Y. Dihydrorhodamine (DHR) test showed poor neutrophil oxidation consistent with X-linked CGD. Definitive microbiologic diagnosis is essential for directing therapy for recurrent bacterial and fungal infections. Treatment of infections should be aggressive. Lifelong bacterial and fungal prophylaxis is necessary for prolonged survival. We report a case of confirmed CGD with the previously unreported mutation.

KEYWORDS:
chronic granulomatous disease, recurrent bacterial infections

INTRODUCTION

Chronic Granulomatous Disease is a rare, inherited disorder of the immune system characterized by the inability of the body's phagocytic cells to make reactive oxygen species (ROS) needed to kill certain microorganisms. As a result, patients have increased susceptibility to infections caused by certain bacteria particularly catalase-producing organisms, mycobacteria, and fungi. Rare infections caused by parasites have been also reported in CGD patients[18]. The usual sites of infection are the skin, lungs, lymph nodes, liver, and bones. The most common genetic type affects only boys, and the disease can vary in its severity. Mutations in all five structural genes that comprise the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase have been found to cause CGD. Hemizygous mutations in *CYBB*, encoding gp91^{phox} are inherited in an X-linked pattern and account for 70% of the cases[2]. The other homozygous or compound heterozygous mutations are autosomal recessive (AR) occurring in both sexes and are associated with a milder disease that may considerably be more frequent in populations where consanguineous marriage practices occur. These mutations affect *CYBA*, *Nthe CF1*, *NCF2* or *NCF4*, encoding p22^{phox}, p47^{phox}, p67^{phox} or p40^{phox} respectively[19,20]. The exact incidence is unknown and the prevalence varies among the populations investigated, from 1 case per 1 million to 1 case per 160,000 individuals internationally[21,22]. A mainstay of therapy is the early diagnosis of infection and prompt, aggressive use of appropriate antibiotics and anti-fungal drugs. The currently only curative treatment of this group is allogeneic hematopoietic stem cell transplantation (HSCT)[23].

CASE REPORT

The patient is a nine-year-old male, Filipino, with a recurrent history of fever. He was born to a 31-year old G_2P_1 (1-0-0-1), who had regular prenatal consultations at a private hospital from the second month of gestation. The mother had cough on the 8th month of gestation but no medication was taken. She also had urinary tract infection on the 9th month for which she took cephalexin for 7 days. The patient was born full-term via caesarian section at the same hospital with Apgar score of 8,9, with clear amniotic fluid. Routine hepatitis B and BCG vaccines were given. Newborn screening was normal. He was noted to have jaundice within 24 hours after birth. There were no other pertinent findings. Complete blood count showed white blood cells of $42x10^9$/L with segmenter predominance (83%). He was given ampicillin and amikacin for 7 days for clinical sepsis as blood culture was negative. A repeat of the white blood cell count showed $18.7x10^9$/L segmenter 51%, lymphocyte 41% and platelet of $271x10^3$/L. He was discharged in improved condition without jaundice. On the 23rd day of life, he started to have intermittent low-grade fever for which paracetamol was given and diarrhea. No other signs or symptoms were noted. He was admitted as a case of late-onset sepsis. CBC showed leukocytosis $35.5x10^9$/L with a predominance of neutrophils (51%) and platelet of $358x10^3$/L. Urinalysis, fecalysis, and blood culture were negative, CSF analysis was normal. He was started on ampicillin and gentamicin then later shifted to cefotaxime. He developed healthcare-associated pneumonia and repeated complete blood counts showed persistent leukocytosis. Chest radiograph showed pneumonia with reactive mediastinal lymphadenopathies. Medications were shifted to meropenem, vancomycin, gentamicin, and metronidazole. On the 3rd week of hospital stay, fever persisted. Repeated chest radiograph revealed the progression of pneumonia with reactive mediastinal lymphadenopathies. Meropenem was shifted to ciprofloxacin. He was given intravenous immunoglobulin (IVIG). Mantoux

test showed no induration. Repeat blood culture was negative, while urine culture grew *Candida albicans*. Hence, amphotericin was started. On the 4th week of admission, the patient remained febrile. He was referred to a hematologist and his bone marrow aspirate showed normal results. He was then transferred to a tertiary center for further work-up.

On physical examination upon transfer, the patient was febrile with oral thrush, crackles, and hepatosplenomegaly. Repeat complete blood count showed leukocytes of $22x10^9$/L, segmenters 64%, lymphocytes 31% and platelets of $457x10^3$/L. Gastric acid-fast bacilli (AFB) stain was negative, 2D-echocardiography was normal, CRP 24 mg/L and ESR 72mm/hr, both elevated. Urine cytomegalovirus culture was negative, as well as CMV and EBV IgM. Urine metabolic screening was also unremarkable. Chest CT scan revealed multiple pulmonary nodules, enlarged mediastinal and hilar lymph nodes. He was started on triple anti-TB regimen. Primary immunodeficiency panel work-up using flow cytometry, immunoglobulin panel, and complement assay were all within normal limits. Nitroblue Tetrazolium Reduction Test was 89% (normal range >80%). He was discharged after 10 weeks. Triple anti-TB treatment was continued at home. A repeat chest CT scan after 1 month of anti-TB treatment showed a decrease in the size of pulmonary nodules, paratracheal, prevascular, subcarinal, subaortic and hilar lymph nodes. Whole abdominal CT scan only showed a prominent left hepatic lobe. The patient continued to have several admissions every month due to recurrent pneumonia. He underwent open lung biopsy, and the findings were consistent with tuberculosis and with noted Periodic Acid Schiff (PAS) test positive for hyphal elements within the cells. He was also a treated as a case of fungal pneumonia. Since his discharge up to his 6th year of age, he had multiple monthly admissions and consultations due to recurrent pneumonia, *Salmonella* sepsis, Herpetic gingivostomatitis, Amoebiasis, Ascariasis, Cervical Lymphadenitis, Infectious diarrhea and oral thrush.

He was also noted to have poor weight gain with a Z-score of <-3. Repeat NBT Reduction Test was still normal at 84%. A DNA analysis was sent to the St. Giles Laboratory of Human Genetics of Infectious Diseases at the Rockefeller University in New York USA, which revealed a previously unreported homozygous mutation in *CYBB,* p.S418Y, possibly related to CGD. Dihydrorhodamine (DHR) test showed poor neutrophil oxidation consistent with X-linked CGD diagnosis. At 7 years of age, there was still intermittent recurrence of fever and diarrhea. He had medical consultations in Singapore where further work-ups were done. T-spot TB was non-reactive and Galactomannan Antigen test was negative. Calprotectin showed elevated results (>300ug/g), which is indicative of an active organic disease with inflammation in the gastrointestinal tract. He was maintained on cotrimoxazole and itraconazole prophylaxis. Since then, he had less sick consults and admissions. Although for the past year, due to the irregular intake of prophylaxis, he was admitted for brain abscess. Cranial CT scan showed multi-loculated brain abscesses with the largest lesion measuring 4.8 x 3.8cm associated with vasogenic edema and subfalcine and uncal herniation. Empiric broad-spectrum antibiotics were started and he underwent emergency right frontal craniectomy and evacuation of the abscess. TB culture, aerobic and anaerobic culture of the abscess were negative. The fungal culture noted filamentous fungus although the final result was negative. Serum galactomannan was 0.59. Voriconazole was added on a suspicion of *Aspergillosis* Chest radiograph showed pulmonary tuberculosis on the right upper lobe. The quadruple anti-TB regimen was also started. Tracheal aspirate culture grew methicillin-resistant *Staphylococcus aureus*. Blood and urine cultures were negative. The patient also developed a catheter-related

infection which grew *Pseudomonas aeruginosa*. The patient eventually improved without deficits. Anti-TB treatment and voriconazole were completed for 6 months. He is currently doing well, on regular follow-ups with few sick consults and with regular intake of cotrimoxazole and itraconazole.

DISCUSSION

CGD is primarily a defect in innate immunity. It was first described in 1957 as a fatal granulomatous disorder. Over the last six decades, it has evolved from an immunodeficiency associated with severe infections with poor prognosis, to a disease with effective management potential and high survival rate[2].

Majority of patients with CGD manifest before the age of 5 and primarily affects males, as most are X-linked. Some may be undiagnosed until adolescence due in part to low index of suspicion. Fungal infections are the leading cause of mortality and are often indolent in their presentation[12]. Response to viral infection is normal. Bacterial infections tend to be symptomatic and are associated with fever and leukocytosis. Pneumonia is the most common presentation followed by abscesses (skin, soft tissue, and organs), suppurative lymphadenitis, osteomyelitis and bacteremia/fungemia. Most of these bacterial infections were seen in this patient. The pathogens responsible for the majority of infections are catalase producing bacteria and various fungi especially *Aspergillus species.* In view of response to voriconazole, the brain abscesses seen were most likely caused by this agent. Non-infectious manifestations also affect patients with CGD. They are prone to granulomata of various organs especially gastrointestinal and genitourinary. Other tissues and organs such as the retina, liver, lungs, and bone may also be affected but reasons are unknown. Oral and non-infectious skin manifestations are usually seen in CGD patients and female carriers of *CYBB* mutation. Our patient frequently has aphthous ulcers, diarrhea, and pulmonary infections Growth delay is common as seen in this patient, and failure to thrive can be a presenting symptom as well as compounded by colitis. Growth may improve in late adolescence and may attain normal predicted weight and height[13].

Diagnosis relies on the direct measurement of superoxide production (NBT)[2] and the use of flow cytometry to measure the production of hydrogen peroxide in the presence of peroxidase. The latter is preferable because of its ability to distinguish the X-linked from the autosomal recessive form of CGD, in general. This patient had NBT test done twice with normal results. Confirmatory tests were done in New York and Singapore led us to the diagnosis of an X-linked CGD with a previously unreported hemizygous mutation in *CYBB,* p.S418Y. Most patients with CGD have mutations in the *CYBB* gene that encodes $gp91^{phox}$, located at Xp21.1[14]. We can only surmise the reasons for the normal NBT test since NBT is limited by its subjectivity, need for an experienced technician, and false-negative results that cause the diagnosis of chronic granulomatous disease to be missed. False-negative findings occur when formazan accumulates in cells with low levels of active NADPH oxidase. These patients clinically have the disease, but their NBT test results are negative[17]. Hence, it is important to pursue further diagnostic tests if the initial test results do not correlate with our patient's condition.

The only routine immunization that CGD patients should not have is BCG as it has been associated with disseminated BCG infection[24]. This patient has received BCG vaccine at birth since it is a WHO-recommended vaccination to all newborns. In retrospect, this patient most likely developed disseminated BCG infection after being vaccinated. As early as 3 weeks old, he already presented with fever, hepatosplenomegaly with multiple

pulmonary nodules, mediastinal and hilar lymph nodes in chest CT scan and lung biopsy results consistent with mycobacterial infection.

Disseminated BCG is extremely difficult to treat and the chance of complete eradication is low unless the functional immune response is restored by hematopoietic stem cell transplant[15]. Multiple BCG reactivations can occur in patients with CGD and BCG can remain latent until reactivations take place in adulthood and manifest as disease[24]. Hence it is important for practitioners to be aware of BCG-related complications, which may be the first sign of an underlying immunodeficiency.

Effective management relies on early diagnosis and aggressive management of infectious complications and lifelong antibacterial and antifungal prophylaxis. Prophylactic trimethoprim/sulfamethoxazole at a dose of 5mg/kg/day divided twice daily reduces the frequency of major infections from one episode every year to one every 3.5 years[9]. Prophylactic itraconazole at a dose of 100mg daily for< 13 years or <50kg and 200mg daily for >13 years or >50kg is effective for reducing the frequency of fungal infections[10]. In a large international multicenter randomized placebo-controlled trial, IFN-y was effective at reducing the number and severity of infections by 70% regardless of inheritance pattern, age or use of prophylactic antibiotics at a dose of 50mcg/m^2 subcutaneously three times per week[11]. Allogeneic hematopoietic stem cell transplant (HSCT) is the only known cure for CGD, but majority survive without it, albeit with co-morbidities[2]. Survival has improved greatly over the last decade and is eminently survivable into adulthood. The survival rate is better for the AR form compared with X-linked CGD[3,4,8,25]. However, $p67^{phox}$ and $p22^{phox}$ AR CGD have similar clinical severity than X-linked CGD[26,27]. Hence, the importance of taking daily preventative medication and monitoring should be emphasized to patients and families.

In summary, this is a case of CGD with a nine-year-old male, who presented with recurrent bacterial and fungal infections that started as early as 3 weeks old. Prolonged, recurrent fever is the most common manifestation noted. Complete laboratory work-ups were done which later confirmed a previously unreported hemizygous mutation in *CYBB,* p.S418Y of an X-linked CGD. He is maintained on antibacterial and antifungal prophylaxis with close follow-up.

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