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CONTENTS

RISK FACTORS IN PREDICTING MORTALITY AMONG CHILDREN ADMITTED FOR PCAP C AND D AT PHILIPPINE CHILDREN'S MEDICAL CENTER

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ABSTRACT

OBJECTIVE: The study aimed to identify risk factors associated with mortality among patients admitted for PCAP C and D.

METHODOLOGY: The study was a cross-sectional study involving children admitted for PCAP C and D at PCMC from January 2017 to December 2019. Univariate and multivariate analyses through binomial logistic regression were used to determine significant predictors of mortality.

RESULTS: A total of 472 patients were included in the study, of whom 77% had PCAP C and 23% had PCAP D. More than half in each patient group were infants; male; and of normal nutritional status. Most common comorbidities in both groups were neurologic and cardiovascular in nature. Leukocytosis, thrombocytosis, and anemia were the most common hematologic findings. Overall mortality rate among patients was 5.08%. On univariate analysis, being severely underweight (cOR 8.28 [95% CI 2.52–27.23]), with history of antibiotic use (cOR 3.01 [95% CI 1.18–7.62], neurologic comorbidities (cOR 4.04 [95% CI 1.42–11.43]), cardiac comorbidities (cOR 5.33 [95% CI 1.31–21.75]), Down syndrome (cOR 22.11 [95% CI 2.44-200.30]), and thrombocytopenia (cOR 22.11 [95% CI 2.44-200.30]) were associated with greater odds of mortality among PCAP-D patients. On multivariate analysis, the odds of mortality were 5.02 (95% CI 1.05-23.96) for severely underweight patients, 4.51 (95% CI 1.13-17.95) in patients with neurologic disease, and 73.62 (95% CI 3.63–1491.10) in patients with Down syndrome.

CONCLUSION: Patients with PCAP D who have severe malnutrition, Down syndrome, cardiac and neurologic abnormalities, and thrombocytopenia should be managed more aggressively to decrease mortality in these patients.

KEYWORDS: PCAP, pediatric, community-acquired pneumonia, mortality

INTRODUCTION

Community-acquired pneumonia (CAP) is a prevalent cause of respiratory morbidity and mortality in a significant part of the global population and is the leading cause of death in children under five years of age. Several clinical practice guidelines have been formulated worldwide, including a local one published by the Philippine Academy of Pediatric Pulmonologists, Inc. in partnership with the Pediatric Infectious Disease Society of the Philippines.

Huang et al found that age < 2 years, pleural effusion as admission diagnosis, Hb < 10 g/dL, WBC count > 17,500/mL, tachypnea, and duration to defervescence >3 days were risk factors for progressive and complicated pneumonia. Streptococcus pneumoniae was the main etiology1. Another study by Koh et al. revealed that presence of co-morbidities and bacteremia were early prognostic variables identified as independent risk factors for poor outcome2. Risk factors identified by Negash et al associated with bacteremic pneumonia were non-vaccination with PCV10, female sex, malnutrition, and chest indrawing, whereas malnutrition was associated with mortality due to CAP3. In a local study by Dembele et al., risk factors significantly associated with death included age of 2–5 months, sensorial changes, severe malnutrition, grunting, central cyanosis, decreased breath sounds, tachypnea, fever (≥38.5°C), saturation of peripheral oxygen <90%, infiltration, consolidation, and pleural effusion on chest radiograph4. Predictors of death were similar in the local study of Lupisan et al which included age 2–5 months, weight for age z-score less than 2 SD, dense infiltrates on chest radiography and definite pathogens isolated in the blood5.

The aim of this study was to create a comprehensive profile of patients with PCAP C and D admitted at PCMC and identify risk factors associated with mortality which may help in guiding optimal utilization of resources for the most effective preventive and early management strategies.

OBJECTIVES OF THE STUDY

General Objective

- To identify risk factors associated with mortality among patients admitted for PCAP C and D at PCMC.

Specific Objectives

1. To determine the demographic characteristics of patients based on the following variables:
    a. Age
    b. Sex

2. To determine the following clinical characteristics:
    a. Nutritional status
    b. Presence of co-morbid conditions
    c. Signs and symptoms
    d.Antibiotics taken prior to admission
    e. Immunization history
    f. Physical exam findings
    g. Laboratory findings (CBC, blood culture, tracheal aspirate culture)
    h. Radiologic findings
    i. Type of admission (ICU or regular ward)
    j. Management (Oxygen support, antibiotics given)
    k. Presence of complications during confinement (development of pleural effusion/ empyema, pneumothorax, lung abscess, chest tube insertion, mechanical ventilation).
    l. Total days confined in the hospital.

3. To determine which of the demographic and clinical characteristics are highly associated with mortality.

METHODOLOGY

This was a cross-sectional analytic study carried out at Philippine Children's Medical Center Quezon City among patients admitted for PCAPC and PCAP D for the years 2017 to 2019.

The participants were cases of PCAP C and D admitted at Philippine Children's Medical Center in Quezon City from January 2017 – December 2019, ages 3 months to 18 years. Exclusion criteria included patients who were (1) immunocompromised, (2) transferees from other hospitals, (3) diagnosed with nosocomial pneumonia. Patients who were immunocompromised were excluded since these patients were more predisposed to developing more invasive infections and can carry poorer outcomes. Those with nosocomial pneumonia were also excluded since hospital acquired infections are largely affected and influenced by hospital infection control measures which is outside the scope of this paper and is not one of the risk factors of interest. Diagnosis and classification of PCAP C and PCAP D was based on the PAPP PCAP 2016 guidelines6.

The study used a simple random sampling method which included patient records for PCAP who were admitted at PCMC for 2017-2019. The number of total PCAP cases which met the inclusion and exclusion criteria were as follows: (1) 218 cases for 2017 (2) 249 cases for 2018; (3) 224 cases for 2019. Based on a national prevalence of 828 per 100,000 population7, the minimum sample size was computed at 158 cases/year.

The information which was included in the data abstraction form were the patients': A. Demographic data (1) age and (2) biological sex. B. Clinical characteristics: (1)history – cough, fever, dyspnea(2) nutritional status9– underweight, normal, overweight, obese (3) co-morbid conditions– cardiac disease, neurologic, chronic lung disease, chronic liver disease (4) antibiotics taken prior to admission (5) immunization history – influenza, pneumococcal, vaccines against Hib and measles (6) physical exam findings– febrile, altered sensorium, signs of dehydration, cyanosis, alar flaring, retractions, crackles, wheeze (7) complete blood count – anemia, thrombocytopenia, thrombocytosis, leukocytosis, leukopenia(8) culture results (blood, tracheal aspirate) (9) chest x-ray findings - interstitial infiltrate, single lobar consolidation, multilobar consolidation, mixed pattern, atelectasis(10) type of admission (ICU or ward) (11) oxygen support – 1-4lpm, 5-15lpm, non-invasive ventilation, intubated (12) antibiotic given; (13) presence of complications (pleural effusion, empyema, pneumothorax, lung abscess, chest tube insertion, mechanical ventilation) (14) total number of hospital days. C. Clinical outcome will be whether (1) discharged or (2) mortality.

Descriptive statistics were used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for nominal

variables, median and range for ordinal variables, and mean and standard deviation for interval/ratio variables. Odds ratios and the corresponding 95% confidence intervals from binary logistic regression were computed to determine the association between clinico-demographic factors and mortality.

All valid data were included in the analysis. Missing data were neither replaced nor estimated. Null hypothesis was rejected at 0.05α-level of significance. STATA 15.0 was used for data analysis.

RESULTS

A total of 472 patients were included in the study, of whom 363 (77%) had PCAP C and 109 (23%) had PCAP D (Table 1). Leukocytosis (39% and 42%), thrombocytosis (27% and 36%), and anemia (23%and 23%) were the most noted hematologic findings among PCAP C and D patients (Table 2). More than half in both groups (60% and 72%) had radiographic readings of infiltrates in both inner and mid lung zones, while more than a third had interstitial infiltrates (36%and 34%). Single lobar consolidation (24% vs 9%) and atelectasis (15% vs 3%) were more common among children with very severe disease. Pleural effusion was the most common lung complication, observed in 1% and 4% of pCAP C and D patients, respectively. One severely ill child developed lung abscess.

The primary sites for care for PCAP-C and PCAP-D patients were the ward and ICU, respectively (Table 3). O2 support of 1-4 lpm was applied to 70.6% of PCAP-C patients, while intubation was applied to 95.4% of patients in the PCAP-D group. For PCAP-D, there were 16 patients with H. influenzae, 6 patients with S. aureus, and 5 patients with S. pneumoniae (Table 4). Blood cultures were likewise positive in below 5% of the patients (Table 5). For PCAP-C, S. pneumoniae and CONS were reported in four patients each, while S. aureus, K. pneumoniae, and Salmonella group D were reported in one patient each. For PCAP-D patients, four patients had CONS, while S. pneumoniae and S. aureus was reported in three patients each. There was one patient with K. pneumoniae in the bloodstream, and one patient positive for Burkholderia. The top five commonly administered antibiotics to PCAP-C patients were: ampicillin (48.21%), ceftriaxone (23.42%), cefuroxime (23.14%), penicillin G (10.47%), and azithromycin (9.37%). The top five commonly administered antibiotics to PCAP-D patients were: ampicillin (75.23%), ceftriaxone (73.39%), gentamycin (32.11%), vancomycin (25.69%), and piperacillin-tazobactam (18.35%) (Table 6). Among PCAP-C patients, less than half (40.2%) had steroids and 78.2% had bronchodilators. Among PCAP-D patients, 66.06% received steroids and 75.23% received bronchodilators (Table 7). Mechanical ventilation and lung abscess as a complication were recorded only in the pCAP D group, in 83% and 1% of its members, respectively (Table 8). Pleural effusion as a complication were observed in both PCAP-C and PCAP-D with 0.83% and 6.42% respectively. Mortality was observed among PCAP-D patients only. Overall mortality rate among patients was 5.08% at

a rate of 0.44 (95% CI 0.29-0.65) per 100 patient-days. Among pCAP D patients, mortality incidence was 22% at a rate of 1.49 (95% CI 1-2.22) per 100 patient-days (Table 10).

On univariate analysis, being severely underweight (cOR 8.28 [95% CI 2.52–27.23]), with history of antibiotic use (cOR 3.01 [95% CI 1.18–7.62], neurologic comorbidities (cOR 4.04 [95% CI 1.42–11.43]), cardiac comorbidities (cOR 5.33 [95% CI 1.31–21.75]), Down syndrome (DS) (cOR 22.11 [95% CI 2.44-200.30]), and thrombocytopenia (cOR 22.11 [95% CI 2.44-200.30]) were associated with greater odds of mortality among PCAP-D patients (Table 11). On the other hand, presence of interstitial infiltrates had decreased the same odds by 79% (95% CI 23%–94%). Signs and symptoms were not included in the univariate and multivariate analysis since some of these are included in the basis of how we classify PCAP-C and PCAP-D. On multivariate analysis, the odds of mortality was 5.02 (95% CI 1.05-23.96) as much in severely underweight patients as in those with normal nutritional status, 4.51 (95% CI 1.13-17.95) with neurologic disease compared to those without, and 73.62 (95% CI 3.63–1491.10) with Down syndrome versus those without (Table 12). This final model explained 37.92% of the variation in mortality ($p < 0.0001$).

DISCUSSION

This study was conducted to identify clinical variables associated with mortality in children with a diagnosis of PCAP C and D. Case fatality rate of childhood pneumonia ranges between 3.4% to 12% in developing countries10. The mortality rate in this study was 5.08%, which is in line with previous published literature. As shown by other publications, young age has been associated with a greater incidence of respiratory infections and tend to be more vulnerable to developing severe pneumonia11. In our study, more than half of each patient group were infants (67% and 72%).

Risk factors for mortality vary between countries and regions due to socioeconomic factors and development in primary health care. In previous studies, younger age, malnutrition, and co-morbid conditions (such as prematurity and congenital heart disease) were found to be significant risk factors11. On univariate analysis, having cardiac comorbidities was one of the risk factors associated with greater odds of mortality among PCAP-D patients. Thrombocytopenia was another risk factor (cOR 22.11 [95% CI 2.44-200.30]). However, this was only seen on univariate analysis although prior studies also had the same findings. Plausible explanation for this is the association of low platelet counts with disseminated intravascular coagulation and severe sepsis13,14. On multivariate analysis, the odds of mortality was 4.51 (95% CI 1.13-17.95) in patients with neurologic disease compared to those without. This is in line with the study of Millman et al where they found that children with neurologic disorders hospitalized with community acquired pneumonia were more likely to be admitted to the ICU than children without neurologic disorders15. Patients with

neurologic co-morbidities —including epilepsy, neurodevelopmental disorders, and neuromuscular disorders—are particularly vulnerable to severe complications and death from respiratory failure since this set of patients may have pulmonary scarring from recurrent aspiration, ineffective cough, and chest wall or spinal abnormalities prohibiting maximal chest expansion15.

Down Syndrome is also one of the risk factors found to be significantly associated with mortality, OR 73.62 (95% CI 3.63–1491.10). The main cause of hospitalization and admission to the pediatric intensive care unit in children with DS is lower respiratory tract infection. Among this set of population, a higher incidence of acute lung injury and acute respiratory distress syndrome is reported. This increased risk of respiratory tract infections and morbidities may be associated with congenital heart disease, abnormal airway anatomy and physiology, hypotonia, and aspiration16. Our result yielded a very wide confidence interval. A possible reason is that we only had a small sample size having only 6 Down Syndrome patients under the PCAP D classification. Deficient nutritional status has clearly been established as a risk factor both for morbidity and mortality among patients with lower respiratory tract infection5,6,17. Similarly, we found that being severely underweight was also strongly associated with a higher likelihood of death based on multivirate analysis (OR 5.02 (95% CI 1.05-23.96)) and was prevalent among PCAP D patients accounting for about 16.5%. The Department of Health has made important efforts to introduce programs for the prevention and management of childhood diseases, examples are promotion of exclusive breastfeeding, supplementation of iron and vitamin A, introduction of EPI, all of which may have an impact on the incidence of new malnutrition cases. However, malnutrition prevalence rates remain high in the Philippines, especially the patients our hospital caters to and unless adequately addressed, will continue to negatively affect the survival of patients with pneumonia.

The results of this study should be viewed considering its limitations. Firstly, because this was a chart review, weight for height which is a better indicator of malnutrition, was not used since most of the data recoverable in the records only included weight. Another limitation was the lack of other potentially relevant risk factors like smoking exposure, lack of breastfeeding, and other socioeconomic factors since this information was also missing. Lastly, microbiological testing was not performed in all patients and viral studies were not done which underestimated the documented etiological agent.

CONCLUSION

In conclusion, the results demonstrated that among children admitted for PCAP D, being severely underweight, having Down syndrome, and having neurologic comorbidities were significantly associated with mortality, and should therefore be managed more aggressively.

TABLES

Table 1. Demographic and clinical profile of children with CAP (n=472)

	pCAP C (n=363)	pCAP D (n=109)
	Frequency (%)	
Age on diagnosis		
Infants (3 months – 2 years)	242 (66.67)	78 (71.56)
Children (2 – 12 years)	117 (32.23)	29 (26.61)
Adolescents (12 – 16 years)	4 (1.10)	2 (1.83)
Sex		
Male	209 (57.58)	63 (57.80)
Female	154 (42.42)	46 (42.20)
Clinical history		
Cough	356 (98.07)	107 (98.17)
Fever	285 (78.51)	81 (74.31)
Cyanosis	6 (1.65)	5 (4.59)
Nutritional status		
Severely underweight	37 (10.19)	18 (16.51)
Underweight	96 (26.45)	28 (25.69)
Normal	217 (59.78)	61 (55.96)
Overweight	12 (3.31)	2 (1.83)
Obese	1 (0.28)	0
Antibiotic use prior to admission	130 (35.81)	37 (33.94)
Physical exam findings		
Dyspnea	250 (68.87)	99 (90.83)
Desaturation	259 (71.35)	100 (91.74)
Hypotension	10 (2.75)	13 (11.93)
Grunting	0	20 (18.35)
Head bobbing	1 (0.28)	19 (17.43)
Altered sensorium	144 (39.67)	98 (89.91)
Irritable	143 (99.31)	71 (72.45)
Lethargic	1 (0.69)	27 (27.55)
Convulsion	5 (1.38)	3 (2.75)
Poor perfusion	1 (0.28)	14 (12.84)
Retractions	309 (85.12)	106 (97.25)
Crackles	329 (90.63)	96 (88.07)
Wheezing	63 (17.36)	23 (21.10)
Rhonchi	29 (7.99)	20 (18.35)
Immunization		
DTwP-IPV-Hib		
None	65 (17.91)	30 (27.52)
Incomplete	166 (45.73)	52 (47.71)
Complete	132 (36.36)	27 (24.77)
PCV		
None	337 (92.84)	103 (94.50)
Incomplete	18 (4.96)	5 (4.59)
Complete	8 (2.20)	1 (0.92)
Influenza vaccine		
None	348 (95.87)	106 (97.25)
Incomplete	8 (2.20)	2 (1.83)
Complete	7 (1.93)	1 (0.92)
Measles/MMR		
None	166 (45.73)	58 (53.21)
Incomplete	129 (35.54)	39 (35.78)
Complete	68 (18.73)	12 (11.01)
Comorbidities		
Cardiac disease	38 (10.47)	6 (5.50)
Neurologic only	38 (10.47)	18 (16.51)
Chronic liver disease (CLD)	12 (3.3)	0
Down Syndrome (DS)	8 (2.20)	2 (1.83)
Asthma	6 (1.65)	1 (0.92)
Bronchiectasis only	1 (0.28)	1 (0.92)
ILD only	1 (0.28)	0
Others	12 (31.58)	10 (9.17)
DS with Cardiac	1 (0.28)	3 (2.75)
Cardiac with other comorbid	3 (0.83)	0
DS with other comorbid	1 (0.28)	0
ILD and bronchiectasis	1 (0.28)	0
Cardiac and Neurologic	1 (0.28)	0
CLD w/ other comorbid	1 (0.28)	0
Neurologic with other comorbid	1 (0.28)	1 (0.92)
DS with cardiac and other	1 (0.28)	0
DS with neurologic and other comorbid	0	1 (0.92)

Table 2. Laboratory and radiologic findings of patients (n=472)

	PCAP C (n=363)	PCAP D (n=109)
	Frequency (%)	
Complete blood count		
Anemia	84 (23.14)	25 (22.94)
Leukocytosis	141 (38.84)	46 (42.20)
Thrombocytosis	98 (27.00)	39 (35.78)
Thrombocytopenia	20 (5.51)	6 (5.50)
Leukopenia	6 (1.65)	2 (1.83)
Chest radiograph		
Interstitial infiltrates	129 (35.54)	37 (33.94)
Infiltrates both inner to mid lung zones	218 (60.06)	78 (71.56)
Single lobar consolidation	33 (9.09)	26 (23.85)
Multi-lobar consolidation	6 (1.65)	3 (2.75)
Mixed pattern	0	0
Hyperinflation	41 (11.29)	15 (13.76)
Perihilar lymphadenopathy	18 (4.96)	2 (1.83)
Atelectasis	11 (3.03)	16 (14.68)
Others	6 (1.65)	1 (0.92)
Radiologic lung complications		
Pleural effusion	5 (1.38)	4 (3.67)
Lung abscess	0	1 (0.92)

Table 3. Type of admission and oxygen support (n=472)

	PCAP C (n=363)	PCAP D (n=109)
	Frequency (%)	
Type of admission		
Ward	363 (100)	4 (3.67)
ICU	0	105 (96.33)
O_2 support		
None	57 (15.70)	0
1-4 lpm	256 (70.52)	0
5-15 lpm	50 (13.77)	4 (3.67)
Non-invasive ventilation	0	1 (0.92)
Intubated	0	104 (95.41)

Table 4. Isolates from tracheal aspirate culture (n=472)

	PCAP D (n=109)
	Frequency (%)
S. pneumoniae	4 (3.67)
S. aureus	3 (2.75)
H. influenzae	12 (11.01)
K. pneumonia	7 (6.42)
P. aeruginosa	5 (4.59)
S. paucimobilis	2 (1.83)
E. aerogenes	2 (1.83)
E. coli	1 (0.92)
M. nonliquefaciens	1 (0.92)
Acinetobacter	3 (2.75)
MRSA	1 (0.92)
H. influenzae, E. coli	2 (1.83)
H. influenzae, C. albicans	1 (0.92)
H. influenzae, K. pneumonia	1 (0.92)
H. influenzae, K. pneumonia, E. coli	1 (0.92)
S. aureus, E. coli	1 (0.92)
S. aureus, MRSA	1 (0.92)
S. aureus, P. aeruginosa	1 (0.92)
S. pneumoniae, S. aureus	1 (0.92)

Table 5. Blood culture profiles in PCAP (n=472)

	PCAP C (n=363)	PCAP D (n=109)
	Frequency (%)	
S. pneumoniae	4 (1.10)	3 (2.75)
S. aureus	1 (0.28)	3 (2.75)
K. pneumoniae	1 (0.28)	1 (0.92)
Coagulase negative *Staphylococcus*	4 (1.10)	4 (3.67)
Burkholderia sp. sp.	0	1 (0.92)
Salmonella group D	1 (0.28)	0

Table 6. Antibiotics given to PCAP C and PCAP D (n=472)

	PCAP C (n=363)	PCAP D (n=109)
	Frequency (%)	
Ampicillin	175 (48.21)	82 (75.23)
Ceftriaxone	85 (23.42)	80 (73.39)
Cefuroxime	84 (23.14)	13 (11.93)
Penicillin G	38 (10.47)	9 (8.26)
Azithromycin	34 (9.37)	18 (16.51)
Gentamicin	19 (5.23)	35 (32.11)
S. Ampicillin	13 (3.58)	7 (6.42)
Piperacillin-tazobactam	11 (3.03)	20 (18.35)
Cefotaxime	6 (1.65)	2 (1.83)
Clindamycin	6 (1.65)	12 (11.01)
Clarithromycin	5 (1.38)	0
Amikacin	4 (1.10)	4 (3.67)
Ciprofloxacin	4 (1.10)	4 (3.67)
Meropenem	4 (1.10)	18 (16.51)
Ceftazidime	3 (0.83)	1 (0.92)
Vancomycin	3 (0.83)	28 (25.69)
Cefepime	1 (0.28)	1 (0.92)
Cefexime	1 (0.28)	0
Cotrimoxazole	0	1 (0.92)
Metronidazole	0	1 (0.92)

Table 7. Other medications for PCAP patients (n=472)

	PCAP C (n=363)	PCAP D (n=109)
	Frequency (%)	
Steroids	146 (40.22)	72 (66.06)
Bronchodilators	284 (78.24)	82 (75.23)

Table 8. Procedures and complications, by CAP severity (n=472)

	PCAP C (n=363)	PCAP D (n=109)
	Frequency (%)	
Interventions		
Mechanical ventilation	0	90 (82.57)
Complications		
Pleural effusion	3 (0.83)	7 (6.42)
Lung abscess	0	1 (0.92)

Table 9. Duration of hospitalization, by CAP severity (n=472)

	PCAP C (n=363)	PCAP D (n=109)
	Frequency (range)	
Duration from onset of symptoms to admission, days	4 (1 – 21)	4 (1 – 24)
Duration of hospitalization, days		
Among survivors	4 (1 – 12)	8 (2 – 15)
Among mortality	-	6 (1 – 21)

Table 10. Mortality incidence and incidence rate, by CAP severity (n=472)

	PCAP C (n=363)	PCAP D (n=109)
	% (95% CI)	
Mortality		
Overall	5.08 (3.28 – 7.47)	
Per group	0 (0 – 1.01)	22.02 (14.65 – 30.97)
Incidence density, per 100 days		
Overall	0.44 (0.29 – 0.65)	
Per group	0	1.49 (1.00 – 2.22)

Table 11. Univariate analysis for mortality among PCAP D patients (n=109)

Variable	Crude Odds Ratio (95% CI)	p-value
Age	1.07 (0.94 to 1.22)	.295
Sex		
Female	Reference	-
Male	1.03 (0.41 to 2.58)	.952
Nutritional status		
Normal	Reference	-
Severely underweight	8.28 (2.52 to 27.23)	.001
Underweight	1.81 (0.56 to 5.82)	.321
Overweight	-	-
Obese	-	-
With history of antibiotic use	3.01 (1.18 to 7.62)	.021
Comorbidities		
Neurologic	4.04 (1.42 to 11.43)	.009
Cardiac	5.33 (1.31 to 21.75)	.020
Down syndrome	22.11 (2.44 to 200.30)	.006
Steroids	0.52 (0.21 to 1.31)	.167
Bronchodilators	0.58 (0.21 to 1.55)	.275
Mechanical ventilation	2.75 (0.59 to 12.85)	.199
Complete blood count		
Anemia	1.53 (0.55 to 4.26)	.413
Leukocytosis	0.78 (0.31 to 1.97)	.598
Thrombocytosis	0.53 (0.19 to 1.46)	0.217
Thrombocytopenia	22.11 (2.44 to 200.30)	.006
Leukopenia	3.65 (0.22 to 60.66)	.366
Chest X-ray		
Interstitial infiltrates	0.21 (0.06 to 0.77)	.019
Infiltrates both inner to mid lung zones	0.96 (0.35 to 2.59)	.929
Single lobar consolidation	2.40 (0.90 to 6.41)	.081
Multi-lobar consolidation	1.80 (0.16 to 20.79)	.636
Hyperinflation	1.35 (0.39 to 4.68)	.641
Atelectasis	2.50 (0.80 to 7.78)	.114
Immunization		
DTwP-IPV-Hib	0.55 (0.21 to 1.43)	.219
PCV	3.90 (0.73 to 20.75)	.110
Influenza vaccine	7.64 (0.66 to 88.13)	.103
Measles/MMR	0.77 (0.31 to 1.92)	.570

Table 12. Multivariate analysis for mortality among PCAP D patients (n=109)

Variable	Adjusted Odds Ratio (95% CI)	p-value
Nutritional status		
Normal	Reference	-
Severely underweight	5.02 (1.05 to 23.96)	.043
Underweight	0.82 (0.16 to 4.32)	.816
Overweight	0	-
Obese	0	-
History of antibiotic use	2.77 (0.76 to 10.14)	.124
Comorbidities		
Neurologic	4.51 (1.13 to 17.95)	.032
Cardiac	0.92 (0.06 to 14.12)	.953
Down syndrome	73.62 (3.63 to 1491.10)	.005
Thrombocytopenia	22.82 (0.93 to 557.77)	.055
Interstitial infiltrates	0.23 (0.04 to 1.38)	107

Adjusted model R^2=37.92%; p <.0001

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IMPACT OF LOW-DOSE HEPARIN ON DURATION OF PERIPHERALLY INSERTED CENTRAL CATHETER AT THE NEONATAL INTENSIVE CARE UNIT: A META-ANALYSIS

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ABSTRACT

OBJECTIVES: To determine efficacy of continuous heparin infusion vs placebo on maintenance of peripherally inserted central catheter line among neonates admitted at the NICU.

METHODS: This is a meta-analysis of randomized controlled trials reported in accordance with PRISMA checklist. Cochrane Risk-of-bias tool was used in assessment of reporting biases. Pooled risk ratios were estimated using random- or fixed-effects model.

RESULTS: Of 4519 studies identified, 4 studies were included, and all have low risk of bias. Meta-analysis showed that continuous heparin infusion on PICCs had significantly higher duration of catheter patency compared to the placebo group (MD=2.22, 95%CI=1.03-3.14, p-value<0.00001). Heparin group also had decreased risk of occlusion (RR=0.47, 95%CI=0.94, p-values=0.03) compared to control. The risk for other adverse events such as thrombosis, infection, IVH progression, and mortality was comparable between the two groups.

CONCLUSION: Continuous heparin infusion in PICC fluids can prolong duration of catheter patency by 2.2 days and reduce risk of catheter-related occlusion by 50%, without having significant effect on incidence of other adverse events.

RECOMMENDATIONS: Continuous heparin infusion on PICC fluids should be part of maintenance and care policy at the NICU, but precautions should be followed to prevent adverse outcomes. Systematic review of intermittent heparin flushing can be a window of opportunity.

KEYWORDS: heparin, peripherally inserted central catheter, patency, neonates.

INTRODUCTION

Intravenous access is an important and crucial part of the neonatal intensive care unit; however nothing can be more difficult, time-consuming and frustrating than obtaining and maintaining a reliable vascular access in newborns. Peripheral intravenous catheters are the easiest and safest means of achieving vascular access. As newborn veins are very tiny, the frequency of cannula change is as high as the incidence of thrombophlebitis. Up to 91% of peripheral lines are removed prematurely due to cannula complications in this population, and peripheral dwell time averages only 27-49 hours (1). Repeated skin breaches expose the vulnerable newborns to infection and painful experiences, which might eventually affect neurodevelopmental outcome. Due to

these factors, maintaining access with peripheral catheters in this population is often difficult and impractical. Therefore, when prolonged support is required, a central line is typically placed. Central venous catheters are considered an indispensable tool in the Neonatal Intensive Care Unit (NICU). Recent technological innovations in catheter size and materials have allowed vascular access in even smaller and sicker infants both for therapeutic and diagnostic purposes, while recognizing its risks to life and limb (2). Preterm and critically ill infants who are slow to tolerate enteral feeds rely highly on venous access for administering fluids, parenteral nutrition, medications, and even blood products, and thus it is vital to their survival. To date, the most frequently used central venous catheters are umbilical vein catheters and peripherally inserted central catheters (PICC).

Peripherally inserted central catheters are routinely used at the NICU, both in term and preterm infants to provide intravenous access for prolonged therapy and parenteral nutrition (3). PICCs are readily available in our setting and can be conveniently inserted at the bedside by trained medical staff without the need for surgical intervention. They are associated with a reduced incidence of complications such as thrombosis, catheter occlusion, and leakage compared to short peripheral catheters (4). Despite these advantages, PICCs are associated with various complications such as occlusion, infection, thrombosis, breakage, migration, and displacement (5). The incidence of PICC-associated complication rates in literature varies from 27-42% (6,7). Collachio stated that most common complication is phlebitis at 32.1%, next is infection at 25.5% and occlusion comes in closely at 17.4%. With regards total parenteral nutrition (TPN) use in the NICU to optimize nutrition for sick neonates, catheter blockage and sepsis are two major complications that have been associated with its administration (8). PICCs have been more prone to possible occlusion and thrombosis than other kinds of central access.

Heparin has been utilized as an antithrombotic agent for maintaining catheters for decades. Anticoagulation effect by heparin is predominantly mediated through antithrombin III in plasma. Due to rapid pharmacokinetics and relatively low cost, heparin is widely and routinely used in clinical practice (9) including among the neonatal population to prevent catheter-related occlusion and malfunction by thrombosis. In some countries and medical facilities, infusion or flushing solutions have become standard procedures. Despite its routine use, several clinical trials studying heparin in catheter maintenance failed to find significance of its efficacy. There are also pressing concerns about the safety of heparin as it has been shown to induce thrombocytopenia, increase bleeding risk, and promote allergic reactions (10). Several randomized trials with inconsistent or conflicting results have been published, prompting further debate on its use for peripherally placed catheter maintenance.

STUDY OBJECTIVES

General Objective:

This study aims to determine the efficacy of continuous heparin infusion on maintenance of peripherally inserted central catheter line among neonates admitted at the Neonatal Intensive Care Unit.

Specific Objectives

1. To determine efficacy of continuous heparin infusion vs placebo on PICC lines at NICU to improve: Mean duration of catheter patency; Catheter-related occlusion incidence rate; Catheter-related thrombosis incidence rate; and Catheter-related bacteremia incidence rate.

2. To determine incidence of adverse events with continuous heparin infusion on PICC lines.

METHODOLOGY

This study employed meta-analysis and reporting was accomplished in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Guidelines. We performed a systematic computerized literature search from various publicly accessible scientific journal databases such as PUBMED, MEDLINE, Cochrane Central Registry of Controlled Trials, and Google Scholar. Database of unpublished trials in https://clinicaltrials.gov, Philippine Health Research Registry, and other foreign clinical trial databases were also checked. Keywords used in the literature search were "peripherally inserted central catheter" or "PICC" or "catheters" [MeSH] and "heparin" [MeSH] and "neonates" or "infant/newborn" [MeSH] or "neonatal intensive care unit" or "intensive care units, neonatal" [MeSH] and "occlusion" [MeSH] or "thrombosis". Neonatology experts were asked for possible reference articles or unpublished studies. Reference and citation lists of the eligible studies have been reviewed also to further look for relevant articles. Duplicate studies were removed, and screening of titles and abstracts was done. Studies were excluding using the inclusion and exclusion criteria and remaining studies were screened using their full text.

Eligibility Criteria

Type of Studies: All prospective randomized controlled trials (from year 2001 to present) determining the effect of heparin infusion on patency of PICC line and other outcomes were included in this meta-analysis.

Type of Participants: All included trials involved neonates (both full term and preterm, regardless of diagnosis and clinical status) on peripherally inserted central catheter lines admitted at the intensive care unit.

Two review authors (primary investigator and co-investigator) independently screened the abstracts and titles of yielded studies with reference to the specified eligibility criteria (see Annex A). No disagreements happened between the reviewers.

Assessment for risk of bias was performed using the Review Manager program, and version 2 of the Cochrane risk-of-bias tool for randomized trials tool (RoB 2.0). Each included article was appraised by the primary investigator and co-investigator based on 5 bias domains: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Co-investigator and research assistant performed data extraction. Extracted data on study design, patient population, facility location, comparator, intervention, and all outcomes measured were recorded and tabulated. The number of central line days, incidence of catheter occlusion, catheter thrombosis, catheter-related infection, and adverse events if any were also recorded on standardized format. Primary outcome pooled in this analysis is the mean duration of catheter patency (in days) for both the intervention group and comparator group. Secondary outcomes collated were the following in each group: incidence of catheter-related occlusion, incidence of catheter-related thrombosis, and catheter-relation bloodstream infection. Adverse events like incidence thrombocytopenia and hemorrhage, if any, were also collated from each study group. The meta-analysis was performed using the Reviewer Manager Software, version 5.3 (Cochrane Collaboration, UK). Relative risk for incidence of catheter-related occlusion, catheter-related thrombosis, and catheter-related bacteremia were estimated, and random effects method was used to estimate the pooled effect. Mean difference for mean duration of catheter patency between the groups was used. Forest plots of the outcomes of interest were generated to display effect estimates and confidence intervals for both individual studies and meta-analysis. The level of statistical significance was set at $p<0.05$, with a 95% confidence interval. To assess heterogeneity between studies for the outcome, chi-squared test was used as included in the forest plot of RevMan program, with $P<0.10$ indicating significant heterogeneity, and I2 with suggested thresholds for low (24-49%), moderate (50-74%) and high (>75%) values. Risk of publication bias was detected with the use of funnel plot.

RESULTS

The initial search through databases and other sources yielded 4,519 references. Most articles were excluded due to different study designs, population, and other outcomes used. Nine full text articles were reviewed for eligibility. Out of the nine, three full text articles were excluded due to a different manner of applying the intervention, one was excluded due to a different catheter used for the patients, and one trial was excluded due to non-availability of study results. A total of four (4) studies were then included in the analysis. A flowchart of study selection is summarized in Figure 1.

This paper included 4 studies, all of which are prospective randomized controlled trials comparing the effect of continuous heparin infusion versus placebo primarily on patency duration of peripherally inserted central catheter amongst neonates admitted at the neonatal

intensive care unit. Two studies were done in 2010 while the other two were done in 2007. For the secondary outcomes, all four studies tested risk for occlusion and bacteremia. Only three studies (Birch, Uslu, and Kamala) analyzed risk for mortality, while only at least two of the four studies tested for the other secondary outcomes like risk for thrombosis, phlebitis, and intraventricular hemorrhage (Table). Risk of bias of the selected articles was judged based on Risk of bias tool (ROB 2.0) and Review Manager 5.0 bias assessment tool. All four included studies in this paper have low risk of bias based on five different domains as summarized in Figure 2.

PRIMARY OUTCOME: Effect of continuous heparin infusion on PICC patency.

Mean duration of catheter patency (in days) for both the intervention group and comparator group was primarily pooled in this study. The overall effect estimate was calculated as mean difference with 95% confidence interval. Pooled summary estimates were derived using the fixed effects method in Review Manager 5.3. Meta-analysis results (Figure 3) indicates that patients with continuous heparin infusion on PICC lines had significantly higher duration of catheter patency compared to the control group (MD=2.22, 95%CI=1.03-3.14, p-value<0.00001). Heparin use can prolong catheter patency by an average of 2.2 days. The level of heterogeneity using I2 is 38% (low).

SECONDARY OUTCOME 1: Relative risk for incidence of catheter-related occlusion and random effects method was used to estimate the pooled effect with 95% confidence interval. Pooled data (Figure 4) showed that there is 50% lower risk for occlusion in the continuous heparin group compared to the control group (RR=0.47, 95%CI=0.94, p-value=0.03). There is moderate heterogeneity (I2 =62%) but visual analysis of the forest plot showed that 3 out of 4 studies leaned more towards heparin than control having less incidence of catheter-related occlusion. Moderate heterogeneity can probably be explained by one study (Birch et al., 2010) leaning more towards control than intervention. A subgroup analysis was done to check for possible causes of heterogeneity by: 1) sample size and 2) heparin dose. Kamala's trial has the smallest sample size and has a different dose of heparin used (1 IU/ml) hence a subgroup analysis excluding this trial was done (Figure 5), however there was even higher heterogeneity (I2 =73%).

SECONDARY OUTCOME 2: Only two of four studies measured risk of thrombosis as their outcome. Relative risk for incidence of catheter-related occlusion and fixed effects method was used to estimate the pooled effect with 95% confidence interval. Pooled data (Figure 6) showed no significant difference between the two groups in terms of risk for thrombosis (RR=0.88, 95%CI=0.51-1.53, p-value=0.65).

SECONDARY OUTCOME 3: All four studies measured risk of sepsis as one of their outcomes. Pooled data (Figure 7) showed no significant difference was observed between the two groups in terms of

risk for catheter-related sepsis or bacteremia (RR=1.01, 95%CI=0.61-1.67, p-values=0.97).

SECONDARY OUTCOME 4: Adverse events noted on the included studies were intraventricular hemorrhage progression, phlebitis, and mortality rate. Two of the four studies measured risk for intraventricular hemorrhage (IVH) (Kamala 2007 and Birch 2010) and risk for phlebitis (Kamala 2007 and Uslu 2010). There was no significant difference in risk for progression of intraventricular hemorrhage (Figure 8, RR=0.52, 95%CI=0.20-1.36, p-value=0.18), and risk for phlebitis (Figure 9, RR=0.80, 95%CI-0.40-1.59, p-value=0.52) between the heparin and control groups.

Three of four studies measured risk for mortality (Kamala 2007, Birch 2010, Uslu 2010), and pooled data shows no significant difference between the intervention and control groups (Figure 10, RR=0.75, 95%CI=0.35-1.64, p-value=0.48). Funnel plot (Figure 11) of the four included studies in this meta-analysis shows a symmetric-shape funnel that indicates publication bias is unlikely.

DISCUSSION

Peripherally inserted central catheters are common in the neonatal intensive care unit for various purposes but is associated with some complications. Most common complications include catheter occlusion prompting its early removal. Heparin is widely used to prevent occlusion however it has also known complications such as allergic reaction, risk of bleeding, and thrombocytopenia. Only a few studies among neonates have been found in literature. Kamala et al. conducted their study on 66 neonates with PICCs used for TPN administration (14). Results showed that the difference in the occurrence of blocked catheters between the two groups was not statistically significant (incidence of 14.3% in heparin group versus 22.6% in no heparin group, p-value= 0.4). A higher percentage (62.9%) of infants in the heparin group received a full course of TPN successfully as compared with those in the no heparin group (48.4%), but this was not statistically significant [relative risk (RR)= 0.6, 95% CI 0.2 to 1.8, p-value= 0.30].

Contradicting results were seen in the study of Shah et al. (19) which compared the usability of PICC when incorporated with heparin amongst a larger sample (201 neonates). The duration of catheter patency was 267 ± 196 hours for the heparin group, while 233 ± 194 hours for the no heparin group (p-value= 0.22). More so, the occlusion rate of the PICC in the heparin group was 6% as compared to the 31% of the no heparin group, which was regarded as statistically significant (p-value= 0.001). Thrombosis and catheter-related sepsis were noted to have no differences (p-value> 0.05), with values of 20% versus 21%, and 10% versus 6%, respectively. The authors concluded that the use of heparin infusion can prolong the duration of peripherally inserted central venous catheter usability, without increasing the incidence of adverse effects. This allows a higher percentage of therapy completion among neonates.

In this meta-analysis, patients who used heparin significantly had longer duration of catheter patency compared to the control group, while the risk for occlusion was also lower. A longer duration of catheter patency for even just +2.2 days will be beneficial for neonatologists as it can make or break the success of their management plan. The risk for other adverse events such as thrombosis, infection, phlebitis, and mortality were comparable between the two groups. The strong evidence shown in this meta-analysis was based on the large effect size (MD=2.22 for duration of catheter patency and RR=0.47 for occlusion), lack of bias in the included studies, and minimal risk for publication bias. These results can be comparable to You's[9] systematic review and meta-analysis which concluded that use of heparin as continuous infusion significantly prolonged the duration of catheter patency (SMD 0.90, 95%CI, 0.48-1.32, $p<0.001$), reduced rates of infusion failure (RR 0.82, 95%CI=0.76-0.92, $p<0.001$) and occlusion (RR 0.82, 95%CI=0.69-0.98, $p<0.05$). But contrary to this meta-analysis, Yao also concluded that risk of phlebitis was significantly decreased with continuous heparin infusion. Studies used in Yao's review were either on intermittent or continuous heparin versus normal saline or placebo on different peripheral intravenous catheters (including PICCs) encompassing all ages (6/32 studies among neonates).

This meta-analysis showed improved outcomes with continuous infusion of heparin; however results must be interpreted with caution since risk for adverse events is still comparable especially among our vulnerable patient population. Recommendation for resuming heparin incorporation to PICC fluids in the NICU is justified but compliance to strict protocols including its dose, manner of preparation, and monitoring is very crucial to achieve target clinical outcomes. This meta-analysis focused on the effect of only one method of heparin incorporation to PICC fluids, which is continuous infusion of heparin. More recent literatures will mention on intermittent heparin incorporation, which is heparin flushing. Important variables like osmolality of fluids or medications infused via PICC, which can be confounding factors in the study results, has not been controlled.

CONCLUSIONS AND RECOMMENDATIONS

Continuous heparin infusion in PICC fluids can prolong duration of catheter patency by an average of two (2) days and reduce the risk of catheter-related occlusion by 50%, without having significant effect on incidence of catheter-related thrombosis, bacteremia, and other adverse events. Catheter occlusion leading to premature removal of PICC has been the unit's primary concern these recent months, and with the overall results of this study, we therefore recommend that continuous heparin infusion on PICC be part of maintenance and care policy at the Neonatal Intensive Care Unit. Just like any other chemical intervention, special precautions should be followed, and subjects monitored for complications to prevent adverse outcomes. Further randomized controlled trials are suggested to explore the benefits of lower dose heparin in discussed outcomes and to study its

economic impact. Systematic review of heparin flushing can also be a window of opportunity.

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Table: Characteristics of Studies Included in the Meta-Analysis

STUDY ID Author, Year, Location	Study Title	Population	Method/Design	Comparator	Intervention (dose)	Study Outcomes
A Kamala, etal. 2007 Kuala Lumpur, Malaysia (Hospital Universiti Kebangsaan Malaysia-NICU)	Randomized controlled trial of heparin for prevention of blockage of peripherally inserted central catheters in neonates	Inclusion: All admitted neonates at NICU with PICC for the purpose of receiving TPN Exclusion: Neonates with clinical evidence of bleeding tendencies, severe IVH Gr3-4, platelet count <100, prolonged APTT	Randomized, double-blind, controlled study	No heparin group	Heparin 1unit/ml	Duration of catheter patency, incidence of catheter blockage, incidence of catheter-related sepsis, IVH, disturbances in lipid metabolism and coagulation studies
B Shah, etal. 2007 Ontario, Canada (4 Tertiary care NICUs)	A Randomized Controlled Trial of Heparin Versus Placebo Infusion to Prolong the Usability of Peripherally Placed Percutaneous Central Venous Catheters (PCVCs) in Neonates:	Inclusion: Neonates requiring percutaneous central venous catheter Exclusion: Grade 3-4 IVH, recent onset presumed/confirmed sepsis, bleeding diathesis, DIC, platelet count <100, preexisting liver disease	Prospective, randomized double-masked, placebo-controlled trial	Placebo (10% or 5% dextrose)	Heparin 0.5 IU/ml	Duration of catheter use, catheter occlusion, catheter-related sepsis, thrombosis, other causes of catheter removal
C Birch, P., etal 2010 New Zealand (Wellington Hospital-NICU)	A randomized, controlled trial of heparin in total parenteral nutrition to prevent sepsis associated with neonatal long lines	Inclusion: Neonates requiring long line for TPN Exclusion: Those with previous long line successfully inserted and utilized	Prospective, randomized, double-blind controlled trial	No heparin	Heparin 0.5 IU/ml	catheter-related sepsis, progression of IVH, Candida line infections, line extravasation OR occlusion
D Uslu, S. etal 2010 Istanbul, Turkey (Diyarbakir Children's Hospital-NICU)	The effect of low-dose heparin on maintaining peripherally inserted percutaneous central venous catheters in neonates	Inclusion: Neonates requiring percutaneous central venous catheter Exclusion: Neonates with bleeding tendencies, Grade 3-4 IVH, recent suspected or confirmed sepsis, thrombocytopenia, DIC, arrhythmia, congenital malformations	Prospective, randomized, controlled, double-blind clinical trial	No heparin	Heparin 0.5 IU/ml	Duration of catheter, phlebitis, infection, blockage, neonatal death

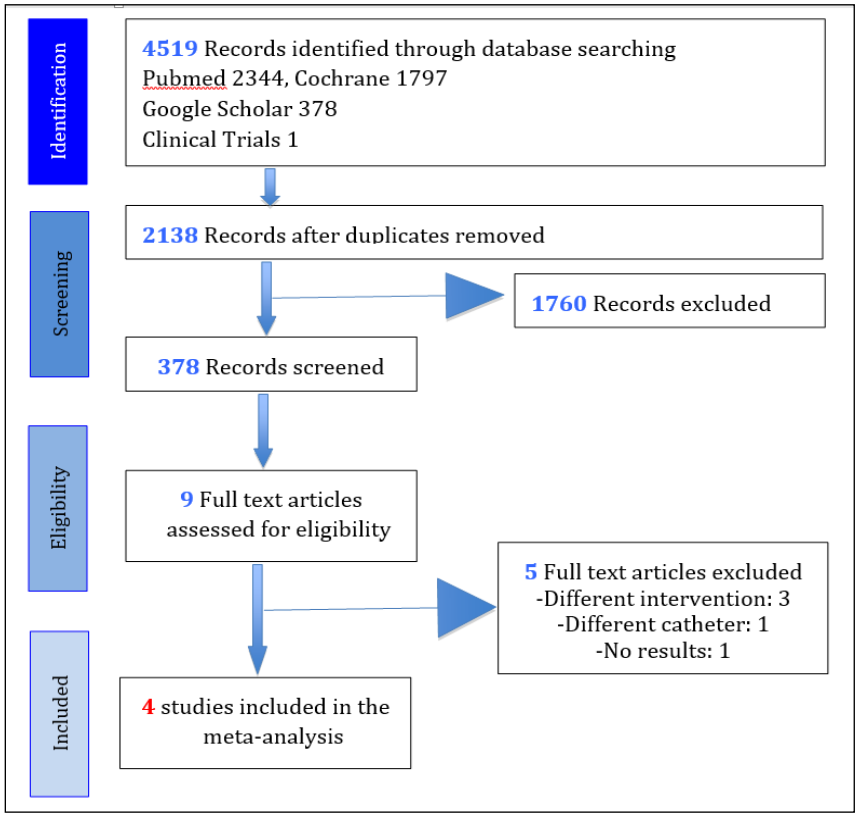

Figure 1: PRISMA Flowchart of Literature Search

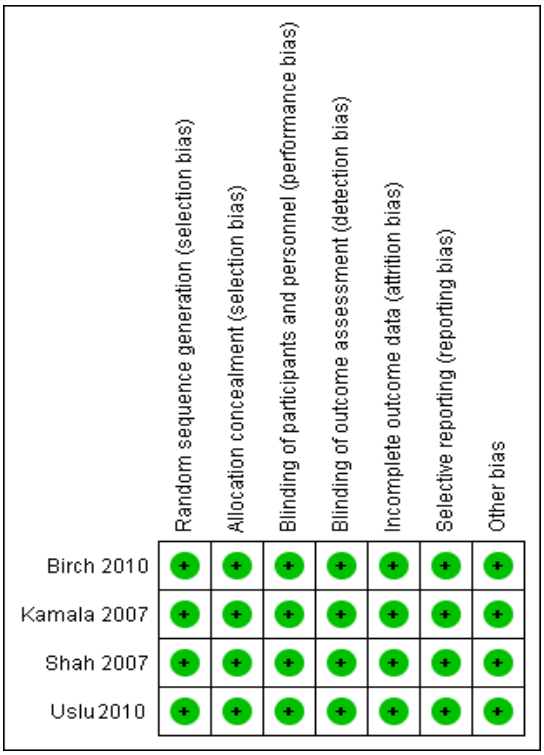

Figure 2. Risk of bias summary of included studies

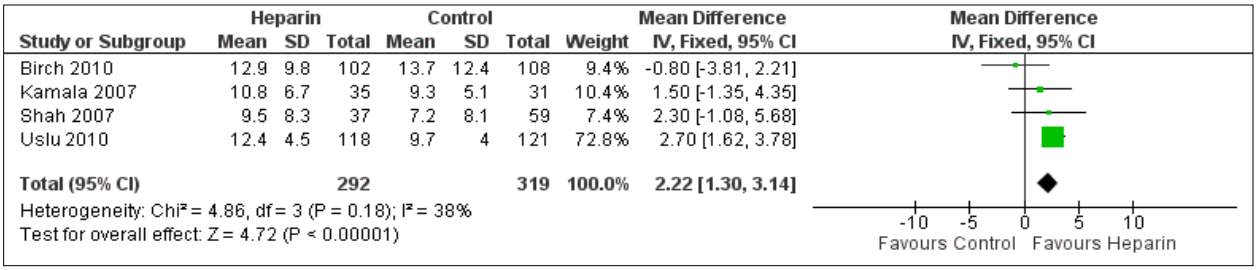

Figure 3: Effect of Heparin on Duration of Catheter patency

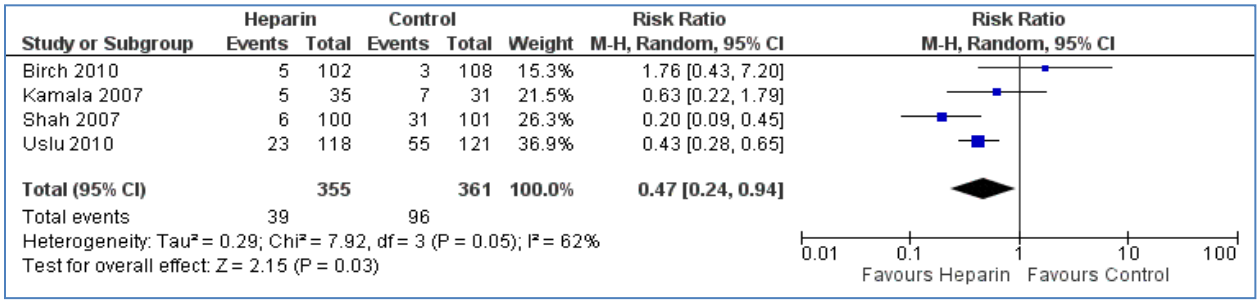

Figure 4: Effect on Heparin on Incidence of Catheter-related occlusion

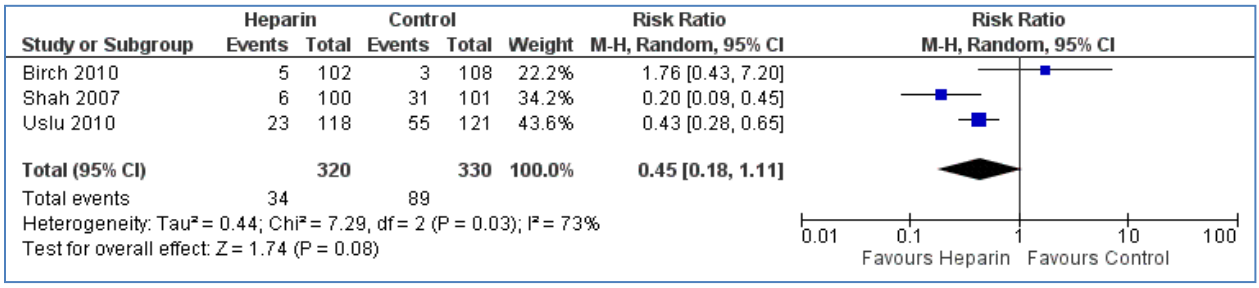

Figure 5: Effect of Heparin on Incidence of Catheter-related occlusion (Subgroup analysis)

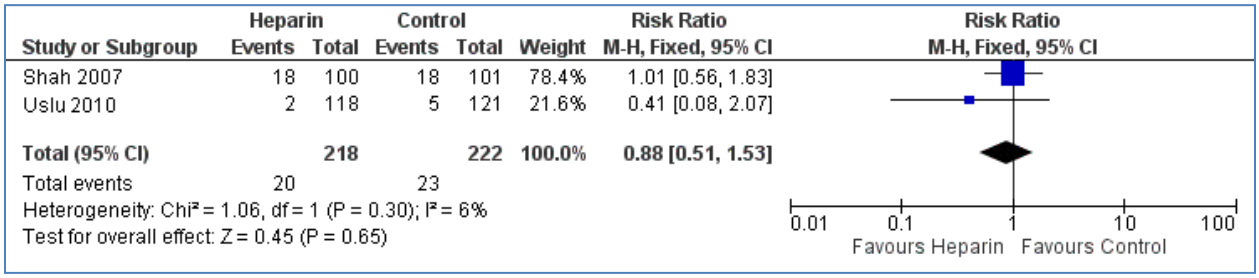

Figure 6: Effect of Heparin on Incidence of Catheter-related thrombosis

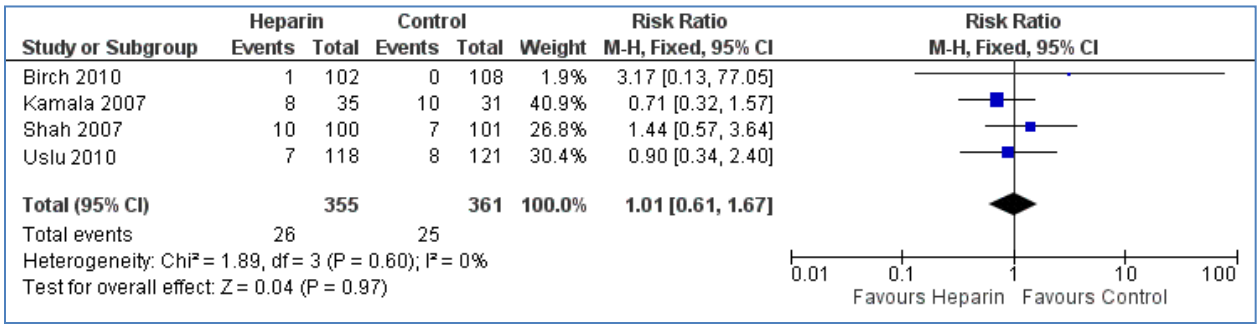

Figure 7: Effect of Heparin on Incidence of Catheter-related bacteremia

Figure 8: Effect of Heparin on risk for IVH progression

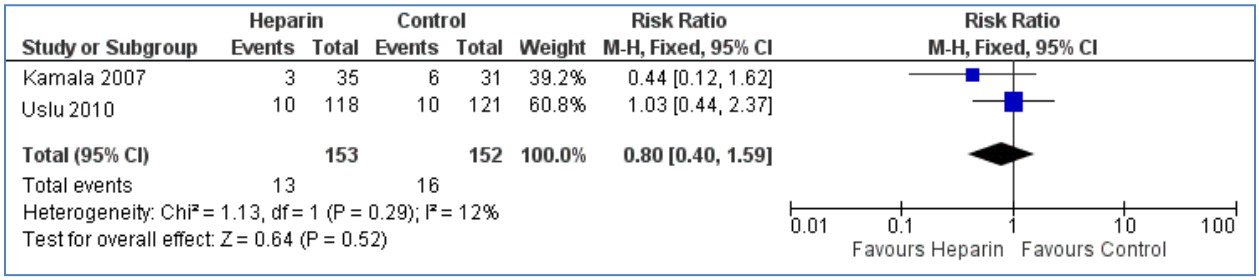

Figure 9: Effect of Heparin on risk for phlebitis

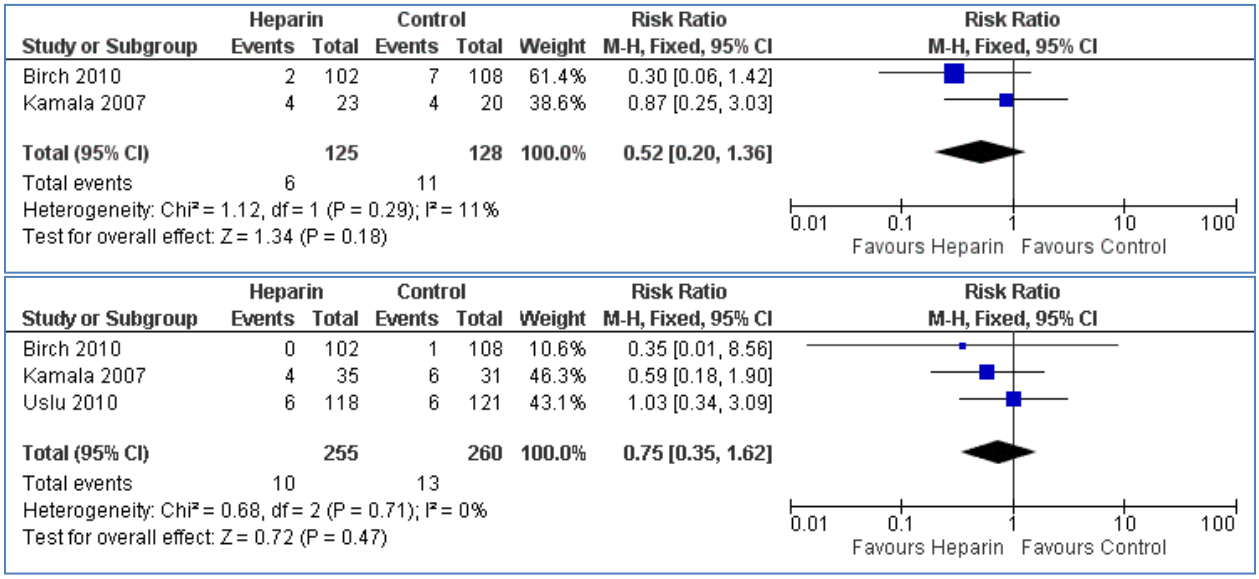

Figure 10: Effect of Heparin on risk for mortality

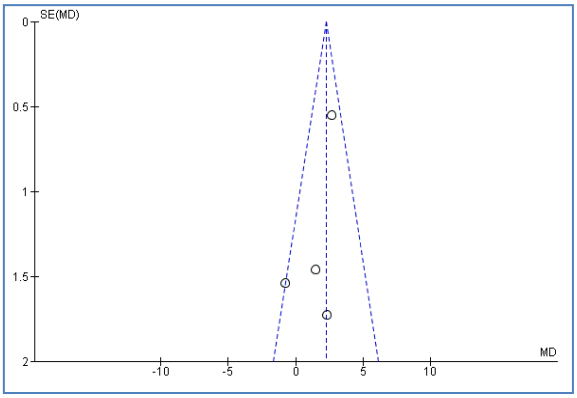

Figure 11: Funnel plot of the included studies

A SYSTEMATIC REVIEW AND META-ANALYSIS ON EFFECTIVENESS OF RICE-BASED ORAL REHYDRATING SOLUTION FOR THE TREATMENT OF ACUTE WATERY DIARRHEA AMONG CHILDREN

MERCELLAINE MARIE S. MANGAHAS, MICHAEL M. RESURRECCION

ABSTRACT

OBJECTIVES: This study aims to compare the effectiveness of rice-based ORS as compared with glucose-based ORS in the treatment of acute watery diarrhea among children. Specifically, it aims to review and analyze the effectiveness of rice-based ORS as compared to glucose-based ORS as to stool output, duration of diarrhea and effect of osmolarity on treatment of diarrhea and to determine associated adverse events associated with rice-based ORS and glucose-based ORS.

METHOD: This study used systemic review and meta-analysis of randomized trials. Primary outcomes were computed with 95% confidence intervals to determine the effectiveness of rice-based ORS. Adverse event was expressed as risk ratios with 95% confidence intervals.

RESULTS: Sixteen studies met the criteria for the systematic review and meta-analysis. Duration of acute diarrhea was shorter by 5 hours with rice-based ORS (MD= −5.27 hours, 95% CI= −9.63 to −0.91, p-value= 0.02) compared to glucose-based ORS. The stool output was 62.35 mL/kg lower with rice-based ORS (MD= −62.35 mL/kg, 95%CI= −128.43 to 3.74, p-value= 0.06) compared to glucose-based ORS. Vomiting was the only reported associated event with ORS intake (RR= 1.08, 95%CI= 0.81to 1.43, p-value= 0.60).

CONCLUSION: Sixteen studies met the criteria for the systematic review and meta-analysis. Duration of acute diarrhea was shorter by 5 hours with rice-based ORS (MD= −5.27 hours, 95% CI= −9.63 to −0.91, p-value= 0.02) compared to glucose-based ORS. The stool output was 62.35 mL/kg lower with rice-based ORS (MD= −62.35 mL/kg, 95%CI= −128.43 to 3.74, p-value= 0.06) compared to glucose-based ORS. Vomiting was the only reported associated event with ORS intake (RR= 1.08, 95%CI= 0.81to 1.43, p-value= 0.60).

KEYWORDS: children, pediatric, oral rehydrating solution, glucose-based ORS, rice-based ORS

INTRODUCTION

The World Health Organization (WHO) reported that globally, there are nearly 1.7 billion cases of childhood diarrheal disease every year.[1] In 2017, diarrhea ranks third as the leading cause of death of children younger than 5.[2] In 2017, the Philippines reported that diarrhea is the cause of death of 3,762 children under five and the death of 473 children 5 to 14 years of age.[3] Oral rehydration therapy (ORT) with glucose and electrolyte solution has been widely recommended by the WHO and United

Nations International Children's Emergency Fund (UNICEF).[4] It is the preferred method to prevent or treat dehydration from diarrhea irrespective of the cause or age. This therapy, together with proper feeding practices was successful to decrease diarrhea-related mortality and malnutrition in the pediatric age group.[5] However, glucose-based ORS is unable to reduce the volume, frequency, and duration of diarrhea.[4] Since the standard ORS with glucose and electrolytes does not impact the progress of the disease, several other interventions have been studied in previous research. The rice-based oral rehydrating solution was introduced to address the limitation of glucose-based ORS. Several clinical trials have shown that rice-based ORS substantially reduces the rate of stool loss. However, other studies have reported no significant benefit. [6,7]

Most clinical guidelines recommend low osmolarity (≤75 mmol/L Na^+) ORS, but lower concentrations of Na^+ have been used successfully.[8] Thus; the optimal composition of ORS is debatable. The advantage of having a single ORS is quite clear and WHO ORS has been the most important preparation achieved by WHO since its formulation. Standard glucose-based ORS has no effect on the duration of the diarrheic stool or the volume of fluid loss. Interventions to improve ORS have included the addition of substrates for sodium co-transport like amino acid glycine, alanine and glutamine. The amino acid preparations have not been demonstrated to be more effective than traditional ORS. [6,7] Other scientists substituted complex carbohydrates for glucose like rice and other cereal based ORS. Studies have shown that protein and amino acid component found in rice- based ORS may result to sodium absorption and the slow breakdown of starch into glucose may stimulate reabsorption of intestinal secretions thus reducing the volume and duration of diarrhea.[9] To date, there have been 3 meta-analyses[9] which aimed to assess the effects of rice-based oral rehydration salts solution compared with glucose-based oral rehydration salts solution on reduction of stool output and duration of acute watery diarrhea.[7, 10] Results showed those who were given rice oral rehydration salts solution had substantially decreased stool outputs than those given oral rehydration salts solution in the first 24 hours. However, most of the included clinical trials in their meta-analysis used ORS ≥ 310 mOsm/L and only a few trials used the newer ORS ≤ 270 mOsm/L, with lower osmolarity. Given the new clinical trials among children conducted since 2016 which included ORS with ≤ 270 osmolarity, the current study aims to synthesize published evidence to determine the effectiveness of rice-based oral rehydration solution for the treatment of diarrhea.

This study aims to compare the effectiveness of rice-based ORS as compared with glucose-based ORS in the treatment of acute watery diarrhea among children. Specifically, it aims to review and analyze the available studies on effectiveness of rice-based ORS as compared to glucose-based ORS as to stool output, duration of diarrhea and effect of osmolarity on treatment of diarrhea and to determine associated adverse events associated with rice-based ORS and glucose-

based ORS. The result of this review can guide the Department of Health (DOH) and health policy makers in the development of guidelines and protocols in the management of acute gastroenteritis in infants and children. The result can direct health leaders to consider intervention that can possibly reduce hospitalization of infants and young children with acute gastroenteritis.

METHODOLOGY

The study used systematic review and meta-analysis. Eligible studies included all randomized trials which determined the effectiveness of rice-based oral rehydration solution in terms of stool output and duration of diarrhea. Studies included were those which used random allocation for patient assignment to either rice-based oral rehydration solution or placebo, control, or standard treatment. The types of participants in the selected studies were infants and children, ages 0 months to 18 years old, with acute watery diarrhea with mild, moderate, or severe dehydration. Excluded participants were those in shock, who cannot drink or take in oral fluids, and with bloody diarrhea. The intervention used in the study was commercially prepared rice-based oral rehydration solution. The studies which assessed the effect of combining rice-based ORS with other solutions were not included. Primary outcomes assessed were total stool output (g/kg) during the first 24 hours after randomization, total stool output (g/kg) from randomization to cessation of diarrhea and duration of diarrhea (hours) from randomization until cessation of diarrhea. Secondary outcome included incidence of adverse events.

The Cochrane Library, PubMed, Medline, EMBASE, and Science Direct were searched using the following keywords: “pediatric" OR “children” OR “oral rehydration solution" OR "ORS" OR "fluid therapy" OR "oral rehydration therapy" OR "oral rehydration" AND "rice". Backward searching of references cited in included studies was also done. Searches covered all studies published from January 1980 until May 2020. Data from studies were extracted into Review Manager (REVMAN 5.3). Information included are author, year of publication, setting, ORS dosage and frequency, type of control group, total sample size, number of patients included, and outcomes reported. The review was done between two reviewers and a dispute was resolved by a third author. The studies were analyzed by primary and secondary outcomes: total stool output (g/kg) during the first 24 hours after randomization, total stool output (g/kg) from randomization to cessation of diarrhea, duration of diarrhea (hours) from randomization until cessation of diarrhea and incidence of adverse events. Pooled estimate of mean difference for primary outcomes was computed with 95% confidence intervals to determine the effectiveness of rice-based ORS. The point estimate of the mean difference (MD) was deemed significant based at the $p < 0.05$ level. Data on adverse events was expressed as risk ratios (RR) with 95% confidence intervals (CI). A morbidity rate per treatment group from each study was used to calculate pooled risk ratios. The point estimate of the risk ratios was considered statistically significant at the $p < 0.05$ level.

Sub-group analyses were done for cholera and non-cholera associated diarrhea and for ORS with ≤ and > 270 osmolarity. The random effects model was used to perform the meta-analysis in the randomized trials. I^2 statistics was used to assess heterogeneity. The reviewers used REVMAN 5.3 in all statistical analyses.

RESULTS

Electronic search yielded a total of 603 articles and 2 identified local studies. A total of 605 articles were screened based on title and abstracts. Twenty relevant articles based on the inclusion criteria qualified for review. Four studies were excluded since outcomes measured did not have mean or standard deviation. Figure 1 outlines the flow diagram based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

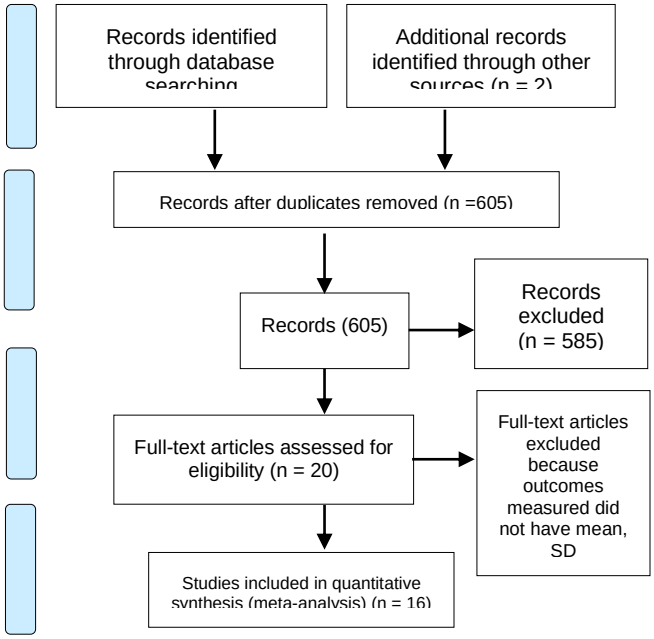

Figure 1. PRISMA Flow Diagram for Study Selection

A total of 16 randomized controlled trials were included in this meta-analysis. The studies were conducted in Bangladesh, Philippines, India, Egypt, Chile, Thailand, Pakistan, Iran, Mexico, Sudan, and Australia. The age ranged between 3 months to 15 years old. The number of samples per study ranged from 20-471. All studies included with patients with acute watery diarrhea of 3 days to less than 1 week duration. Five of the studies enrolled patients with severe dehydration and 10 other studies enrolled with mild to moderate dehydration. Three studies identified the pathogen causing diarrhea in their participants.[b,c,i] Only 4 studies compared rice-based ORS with glucose-based ORS with osmolarity ≤ 270 mOsm/L.[a,b,h]

Table 1. Summary of characteristics of included studies

Author, year	Study Design and Setting	Participants	Cause of Diarrhea	Interventions
Alam, 1987	RCT Hospital-based trial in Bangladesh	N=72 Aged 1 to 8 years; with watery diarrhea < 3 days; presence of moderate to severe dehydration;	Pathogen not mentioned	• Glucose ORS, n=30 (≥ 310 mOsm/L) • Rice ORS, n=30
Calimlim, 2014[a]	RCT Hospital-based trialin Philippines	N=130 Age 6 months to 5 years; acute watery diarrhea < 1 week; any dehydration	Pathogen not mentioned	• Glucose ORS + Zinc, n=64 (≤ 270 mOsm/L) • Rice ORS + Zinc, n=66
Dutta, 1998	RCT Hospital-based trial in India	N=20 Age 3 to 12 years; acute watery diarrhea; severe dehydration	Pathogen not mentioned	• Glucose ORS, n=30 (≥ 310 mOsm/L) • Rice ORS, n=30
Dutta, 2000[b]	RCT Hospital-based trial in India	N=58 Age 2 to 10 years; acute watery diarrhea; severe dehydration	*V. cholerae*	• Glucose ORS, n=20 (≥ 310 mOsm/L) • Glucose ORS, n=19 (≤ 270 mOsm/L) •Rice ORS with electrolyte content of glucose ORS ≤ 270, n=19
el-Mougi, 1996[c]	RCT Hospital-based trial in Egypt	N=89 Age 3 to 24 months; acute watery diarrhea; mild to moderate dehydration	Non-*V. cholerae*	• Glucose ORS, n=44 (≥ 310 mOsm/L) •Rice powder ORS, n=45
Faruque, 1997	RCT Hospital-based trial in Bangladesh	N=471 Age 3 to 35 months; acute watery diarrhea; mild to moderate dehydration	Pathogen not mentioned	• Glucose ORS, n=235 (≥ 310 mOsm/L) •Rice powder ORS, n=236
Fayad, 1993[d]	RCT Hospital-based trial in Egypt	N=441 Age 3 to 18 months; acute watery diarrhea < 1 week; with any dehydration	Pathogen not mentioned	• Glucose ORS, n=222 (≥ 310 mOsm/L) •Rice ORS, n=219
Guiraldes, 1995[e]	RCT Hospital-based trial in Chile	N=48 Age 3 to 24 months; acute watery diarrhea; moderate dehydration	Pathogen not mentioned	• Glucose ORS, n=24 (≥ 310 mOsm/L) • Rice ORS, n=24
Islam, 1994	RCT Hospital-based trial in Pakistan	N=452 Age less than 6 months; acute watery diarrhea; mild to moderate dehydration	Pathogen not mentioned	• Glucose ORS, n=20 (≥ 310 mOsm/L) •Rice ORS, n=20

Kianmehr, 2016[f]	RCT Hospital-based trial In Iran	N=40 Age 8 to 24 months; acute watery diarrhea; any dehydration	Pathogen not mentioned	• Glucose ORS, n=48 (≥ 310 mOsm/L) •Rice ORS, n=49
Maulen-Radovan, 1994[g]	RCT Hospital-based trial in Mexico	N=97 Age 1 to 6 months; acute watery diarrhea < 5 days; mild to moderate dehydration	Pathogen not mentioned	• Glucose ORS, n=48 (≥ 310 mOsm/L) •Rice ORS, n=49
Maulen-Radovan, 2004[h]	RCT Hospital-based trial in Mexico	N=189 Age 2 to 24 months; acute watery diarrhea < 5 days; males only; any dehydration	Pathogen not mentioned	• Glucose ORS, n=92 (≤ 270 mOsm/L) •Rice ORS, n=97
Mustafa, 1995	RCT Hospital-based trial in Sudan	N=96 Age less than 5 years; acute watery diarrhea; males only; moderate to severe dehydration	Pathogen not mentioned	• Glucose ORS, n=30 (≥ 310 mOsm/L) •Rice ORS, n=32
Wall, 1997	RCT Hospital-based trial in Australia	N=100 Age 4 weeks to 5 years; acute watery diarrhea; mild to moderate dehydration	Pathogen not mentioned	• Glucose ORS, n=50 (≥ 310 mOsm/L) •Rice ORS, n=50
Zaman, 2001[i]	RCT Hospital-based trial in Bangladesh	N=167 Age 5 to 15 years; acute watery diarrhea; moderate to severe dehydration	*V. cholerae*	• Glucose ORS, n=82 (≥ 310 mOsm/L) •Rice ORS, n=85

As seen in Figure 2, all the trials employed randomization in patient allocation into treatment groups. Thirteen papers (80%) of the trials described their randomization process. Twenty percent of included studies described their allocation concealment. Blinding of participants and/ or personnel were done in 25% of the trials.[d,e,f,g] All of the studies have low risk for attrition, reporting and other biases.

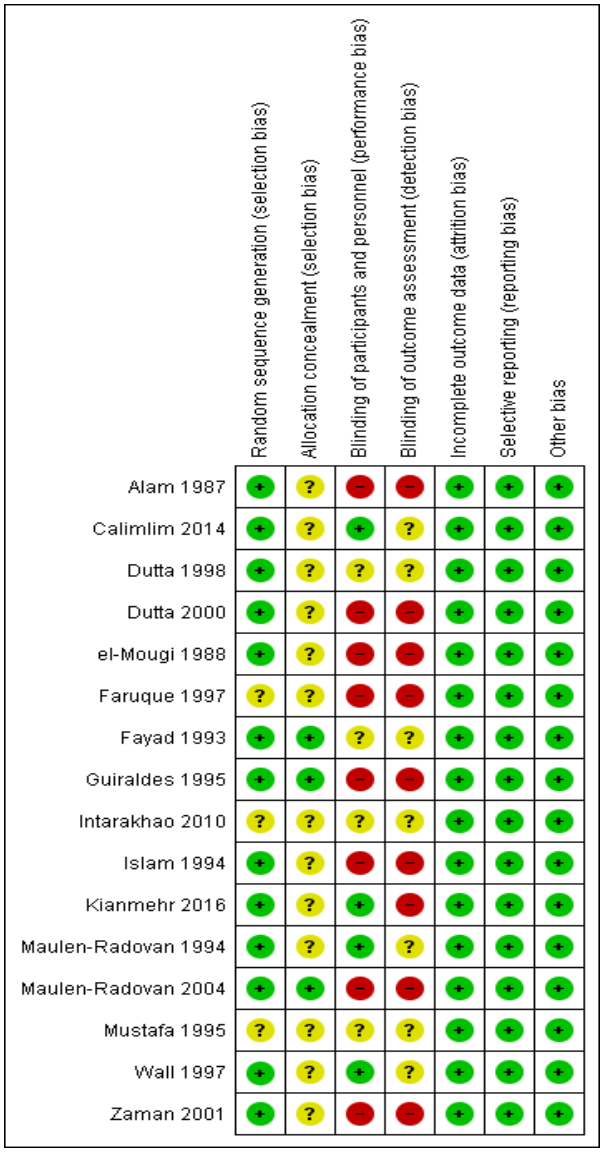

Figure 2. Risk of bias summary

Effectiveness of rice-based ORS for the treatment of diarrhea

Across 14 trials, the average duration of diarrhea was significantly shorter by 5 hours in the rice-based ORS groups (MD= −5.27 hours, 95% CI= −9.63 to −0.91, p-value= 0.02) compared to glucose-based ORS. There was substantial heterogeneity among the trials (Chi² test p-value< 0.00001, I² statistic= 99%). Sub-group analyses by osmolarity of glucose-based ORS comparator showed that on average across four trials, (MD= −8.27 hours, 95%CI= −16.19 to −0.35, p-value= 0.04) compared to glucose-based ORS with osmolarity ≤ 270 mOsm/L. There was still substantial heterogeneity among the trials (Chi² test p-value< 0.00001, I² statistic= 94%). In comparison, the duration of diarrhea was 4 hours shorter with rice-based ORS (MD= −4.02 hours, 95%CI= −9.17 to 1.13, p-value= 0.13) compared to glucose-based ORS with osmolarity ≥ 310 mOsm/L, but this was not statistically significant. There was substantial heterogeneity among the trials (Chi² test p-value< 0.00001, I² statistic= 99%). The funnel plot suggests no risk for publication bias.

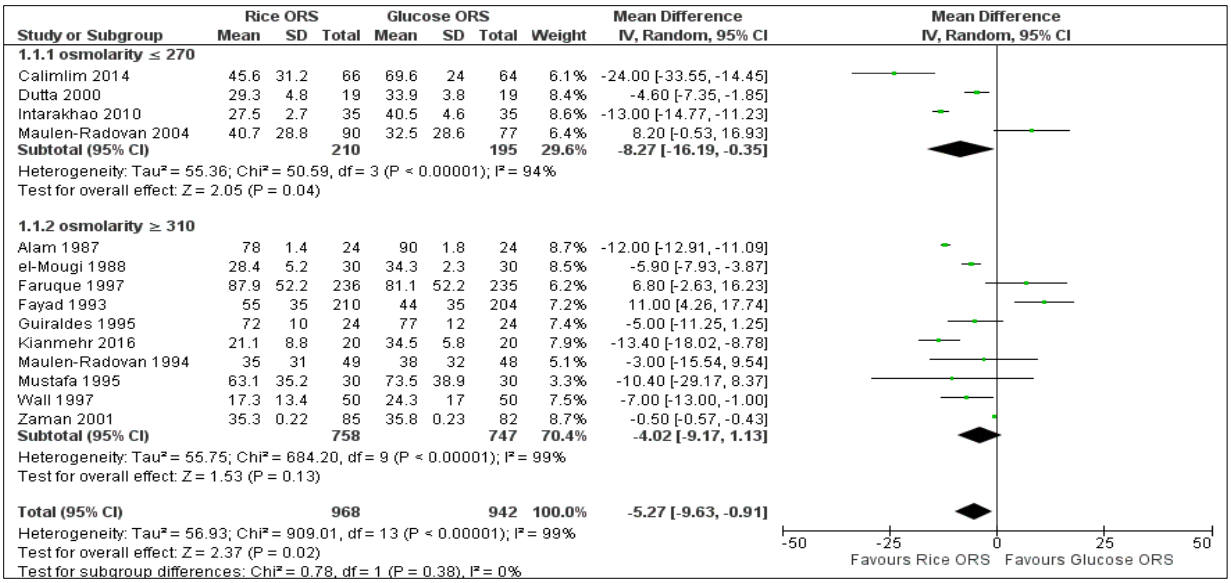

Figure 3. Random effects meta-analysis on the effect of rice-based ORS versus glucose-based ORS in duration of diarrhea

Across five trials, stool output was 62.35 mL/kg lower with rice-based ORS (MD= −62.35 mL/kg, 95%CI= −128.43 to 3.74, p-value= 0.06) compared to glucose-based ORS with osmolarity ≥ 310 mOsm/L, but this was not statistically significant. There was substantial heterogeneity among the trials (Chi² test p-value< 0.00001, I² statistic= 100%). None of the studies with glucose-based comparator with osmolarity ≤ 270 mOsm/L reported on stool output. The funnel plot suggests no risk for publication bias.

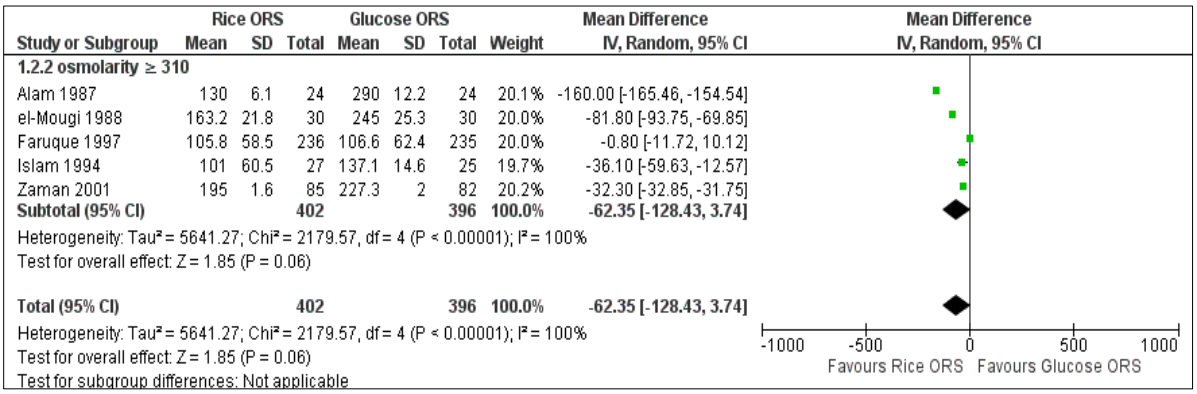

Figure 4. Random effects meta-analysis on the effect of rice-based ORS versus glucose-based ORS in stool output for the first 24 hours

Among five studies which reported adverse events, vomiting was the only reported associated event with ORS intake. Upon analysis, there was no significant difference between the rice-based and glucose-based ORS groups with osmolarity

≥ 310 mOsm/L in the risk of vomiting (RR= 1.08, 95%CI= 0.81to 1.43, p-value= 0.60). The trials were homogenous (Chi² test p-value< 0.56, I² statistic= 0%). None of the studies with glucose-based comparator with osmolarity ≤ 270 mOsm/L reported on the risk of vomiting. The funnel plot suggests no risk for publication bias.

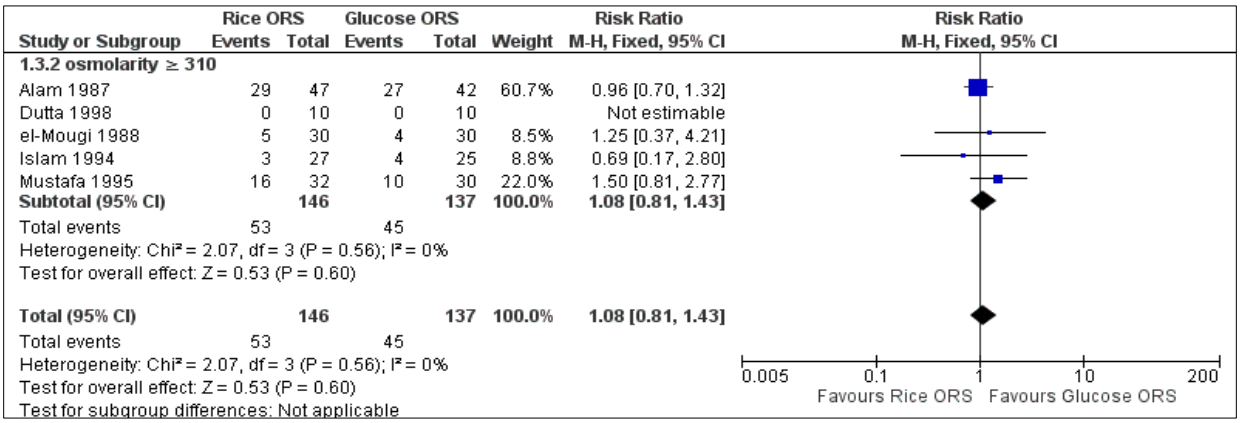

Figure 5. Random effects meta-analysis on the risk of adverse events of using rice-based ORS versus glucose-based ORS

DISCUSSION

Acute gastroenteritis (AGE) is a major cause of mortality and morbidity globally among infants and children under 5 years of age, especially in low-income countries. Oral rehydration solution (ORS) is universally recognized as first-line treatment of AGE, and it is mainly used to replace the electrolytes lost in stools in diarrheal episodes. However, standard glucose-based ORS was not seen to demonstrate reduction of volume, frequency, and duration of diarrhea.4 This study was done to determine whether the alternative rice-based ORS will be more effective in the treatment of acute diarrhea as compared to glucose-based ORS.

In this meta-analysis, the duration of diarrhea was significantly shorter by 5 hours with rice-based ORS compared with glucose-based ORS (p = 0.02). The effect on duration of diarrhea was more pronounced upon comparison of rice-based ORS to the low osmolarity glucose-based ORS where the duration was shortened by 8 hours. However, upon comparison of the effect of standard osmolarity glucose-based ORS and rice-based ORS, there was no significant difference seen (p = 0.13). The faster absorption with the rice powder may be associated with the shorter duration of the diarrhea. The shorter duration of diarrhea seen with the supplementation of rice-based ORS could be beneficial for patients who are admitted for observation in a hospital setting. Stool output was not significantly different between rice-based ORS and glucose-based ORS. However, stool output was lower by 62.35 mL/kg with the use of the rice-based ORS compared with glucose-based ORS. The clinical significance of this finding suggests the utility of rice-based ORS in preventing dehydration for smaller infants.

Identified adverse event in ORS supplementation included the risk of vomiting during the early period of rehydration, with some participants had persistent vomiting, which was found to be not statistically significant (p = 0.60). The glucose concentration increases the osmotic load which aggravates the fluid loss.

The results, however, were highly heterogenous despite the conduct of sub-group analyses. This may be attributed to diversity in the methodology especially with regards to study population and method of assessing the outcomes. The quality of evidence also is low due to the unreported methodology of randomization and allocation concealment. Blinding was also not performed which may results to measurement and performance bias. There was serious risk of indirectness as all trials were conducted in a hospital setting and results may not be generalizable in the community setting. There was also risk of imprecision due to the small sample size and wide confidence interval (CI) of the pooled estimate. In terms of stool output and risk for vomiting, no significant differences were also observed.

The results of the study which favored the use of rice-based ORS over glucose-based ORS in the treatment of diarrhea was consistent with a previous meta-analysis involving children by Gregorio, et al.9 With the results of the study, the researcher recommends the use of rice-based ORS in patients with acute diarrhea. The Department of Health (DOH) can make use of the rice-based ORS in making new guidelines and protocols in the management of acute diarrhea in infants and children. The results can direct health leaders to consider intervention that can possibly reduce hospitalization of infants and young children with acute diarrhea.

CONCLUSION & RECOMMENDATIONS

Rice-based ORS show advantage in reducing the duration of diarrhea among children when compared to glucose-based ORS. Although there was no significant difference on reduction of stool output between rice-based ORS and glucose-based ORS, the reduction of stool output by 62.35 mL/kg seen in rice-based ORS may be clinically important in managing acute diarrhea for infants. All studies included supported that rice-based ORS is safe and tolerable. With the high heterogeneity of the data gathered in this study, it is recommended to have more randomized controlled trials with large sample size to provide conclusive evidence on the effectiveness of rice-based ORS among children. It is also recommended to compare the effect of rice-based ORS on different pediatric age groups.

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FACTORS AFFECTING PROLONGED HOSPITALIZATION IN CHILDREN 6 MONTHS TO 5 YEARS WITH SEVERE COMMUNITY ACQUIRED PNEUMONIA

MA. KRISTEL M. NADLANG, MARIA EVA I. JOPSON

ABSTRACT

OBJECTIVE: To determine the factors affecting prolonged hospitalization in children 6 months to 5 years diagnosed with severe pneumonia.

METHODOLOGY: The study was a retrospective chart review of patients aged 6 months to 5 years diagnosed with Severe Community Acquired Pneumonia and admitted at the Philippine Children's Medical Center over a 24-month period from January 2018 to December 2019. Variables such as the age and gender of the child, immunization and socio-economic status as well as presence of hypoxemia, respiratory rate on admission, nutritional status and number of antibiotics were correlated with the duration of stay.

RESULTS: Younger age, low socioeconomic status and greater number of antibiotics used were found to be significantly associated with prolonged duration of hospital stay after controlling for other variables.

CONCLUSION: Findings in this study can help pediatricians to identify children with severe pneumonia who will likely need to be admitted for a prolonged period of time.

KEYWORDS: *community acquired, pneumonia, prolonged hospitalization*

INTRODUCTION

Pneumonia is an infectious disease of the lower respiratory tract that is a leading cause of morbidity and mortality among children under five years of age worldwide. Globally, there are over 1,400 cases of pneumonia per 100,000 children, or one case per 71 children every year, with the greatest incidence occurring in resource-limited regions. Recent data from the United Nations International Children's Emergency Fund (UNICEF) show that it is still the leading infectious cause of death among children under five years old claiming the lives of over 800,000 children every year, or around 2,200 every day in 2018. (1) In the Philippines, pneumonia is ranked ninth among the ten leading causes of morbidity across all age groups. As for the local incidence, estimates from Department of Health (DOH) in 2010 showed that there were approximately 381,123 (or 412.8 per 100, 000) cases with 197, 852 cases (52%) occurring in the age group of 1 to 4 years old. (2) Thus, pneumonia continues to be a major reason for hospitalizations in this vulnerable age group. In resource-poor countries like the Philippines, the economic burden of this disease cannot be overemphasized. (3)

Because of this economic impact on caregivers, the physician's clinical

assessment of the child diagnosed with pneumonia should be done in a thorough manner through complete history and physical examination to determine the severity of his/her condition. By determining those children with severe pneumonia, appropriate treatment and management can be instituted in a timely manner and they could be discharged well without any sequelae. Among the important outcomes is prolonged hospitalization or length of stay, which takes a toll on the parents' financial capabilities in caring for the sick child. Recent estimates from the US Centers for Disease Control and Prevention (CDC) showed that the average length of hospital stay for treatment of pneumonia in children less than 15 years of age (excluding neonates) is five days. (4) Prolonged hospitalization, therefore, can be considered when a patient exceeds hospital stay of more than 5 days. Studies exploring predictors of prolonged hospitalization among children diagnosed with community acquire pneumonia have been scarce. Literature search only yielded a single study by Kuti and colleagues in 2014 conducted in a rural health center in Gambia. (5) With prolonged hospital stay due to severe pneumonia, the caregivers may have to resort to "out-of-pocket" payment when the insurance coverage has been maxed out. As a result of the extended days receiving treatment in a health facility, the economic burden on the families taking care of children with a severe course of pneumonia will be exacerbated. By mere identification of the children afflicted with severe pneumonia who will most likely need extended hospitalization, the parents or guardians can be advised well and they can be prepared beforehand of the possible additional costs to be taken into account. With that, they will be able to mobilize their resources in order to provide financially for the recovery of their sick patients.

This research study aims to identify the factors affecting prolonged hospitalization in children six months to five years diagnosed with Community Acquired Pneumonia Severe according to the World Health Organization (WHO) definition and who were admitted at Philippine Children's Medical Center (PCMC). Specifically we aimed to describe the sociodemographic profile of these children as to their age, sex, immunization status and socio-economic status; to identify the clinical features at presentation of the child as to hypoxemia on pulse oximetry reading, respiratory rate on admission, nutritional status and number of antibiotics used; and to determine the association between clinical features at presentation with prolonged hospitalization of children with severe community acquired pneumonia. The information derived from this study can help pediatricians to identify children with severe pneumonia who will likely need to be admitted for a prolonged period of time given that they possess significant sociodemographic factors or clinical features upon initial presentation at the hospital. The findings of the research will also help the clinicians to apprise parents/guardians of the severity of the patient's pneumonia and that prolonged hospitalization may bring about additional financial constraints. This can help them make decisions and find solutions to the problems that may arise in caring for the

sick child. They will be more prepared to mobilize resources in order to cope with the burden of shouldering additional costs that cannot be covered anymore by the health insurance if applicable.

Materials and Methods

This was a cross sectional analytical retrospective study of patients aged six months to five years diagnosed with Severe Community Acquired Pneumonia/Pediatric Community Acquired Pneumonia C and admitted at the Philippine Children's Medical Center over a 24-month period from the month of January 2018 to December 2019. Those admitted to the ICU or were intubated were excluded from the study due to presumed extended stay in the hospital. The target population consisted of all the children aged six months to five years discharged with a final diagnosis of Severe Community Acquired Pneumonia or Pediatric Community Acquired Pneumonia C with International Classification of Diseases (ICD)-10 code of J18.92 during a two-year period.

Sample size calculation for logistic regression to identify prognostic factors was based on the work of Peduzzi et al. (1996):

> **p** is the smallest of the proportions of negative or positive cases in the population
>
> **k** is the number of covariates (the number of independent variables) **minimum number of cases to include is: N = 10 k / p**

For this study, eight covariates were included. A proportion of 25.0% (105/420) was used for prevalence of prolonged hospital stay among those with childhood pneumonia based on the study of Kuti et al (2014). The minimum number of cases required was: N = 10 x 8 / 0.25 = 320.

The study was conducted from July 2020 to October 2020. The Pneumonia Registry of the PCMC Medical Records section was accessed for this purpose. From there, cases diagnosed with severe community acquired pneumonia/Pediatric Community Acquired Pneumonia C or those with ICD code of J18.92 were included. Simple random sampling was done using a computer-generated table. Those with missing data on the chart were excluded from the final sample. Data gathered included sociodemographic data such as the age and sex of the child, immunization status and socio-economic status. Classification of the immunization status of the participants was determined following the vaccination schedule recommended for age by the Pediatric Infectious Diseases Society of the Philippines either as complete or incomplete. Socio-economic status was obtained using the information available in the admitting form. Those who were classified as "Service" came from low income families and those who were classified as "Pay" came from high income families. The chart review included clinical features at initial presentation: hypoxemia, respiratory rate on admission, nutritional status, and number of antibiotics. The nutritional statuses of the children were based on the weight and height recorded on the chart. Body mass index (BMI) was also

determined, and the values were then plotted for age using the WHO growth charts and interpreted accordingly.

The analysis of the data was calculated using frequencies and percentages. The data were entered in Microsoft Excel worksheet and analyzed with SPSS Version 17.0. Differences between continuous variables were determined using Student's t-test for normally distributed variables. The level of significance at a 95% confidence interval (CI) was set at $p<0.05$. Associations between dependent (prolonged hospital stay) and independent variables (risk factors) were assessed using univariate analysis. To find out the independent contribution of each factor towards the outcome, multivariate logistic regression analysis was used. Those that gave significant results were used in the multivariate analysis to determine their independent effects on dependent variables. Results were interpreted with odds ratios (ORs) and 95% CIs. Statistical significance was established when the CI did not embrace unity. The study was submitted to the PCMC Institutional Review Ethics Committee (IREC) and was approved prior to commencement and data collection.

RESULTS

Table 1 shows the socio-demographic characteristics of the children included in this study. A total of 320 children diagnosed with Severe Community Acquired Pneumonia from January 2018 to December 2019, with age six months to five years old were included in the study. More than half of the children were within the 1-5 years old age group (68%) and were mostly males (61%). Furthermore, as high as 87% of the children included in the study had incomplete vaccination for age based on Childhood Vaccination Schedule set by the PIDSP. Seventy percent of the children belong to low income families.

Table 2 shows the association between the socio-demographic characteristics and the duration of hospital stay. Less than half (41%) had prolonged hospital stay of more than five days and majority were males (61.4%). The younger age group (6-11 months) and low socioeconomic status were also significantly associated with prolonged duration of hospital stay (both at p-value<0.001). There was a higher proportion patients with low socioeconomic status in those who had prolonged hospital stay (83.3%) compared to those with shorter hospital stay (61.2%). On the other hand, the other variables (Sex and vaccination status) were not significantly associated with duration of hospital stay.

Table 3 shows the association between the clinical features of the patients at presentation and the duration of hospital stay. Incidence of hypoxemia (oxygen saturation of < or = 94%) was significantly associated with prolonged duration of stay (p-value=0.004). However, having a respiratory rate > 70 upon assessment on admission of the child was not found to be significantly associated with duration of hospitalization.

Being underweight (z scores below -2 on the WHO weight for age growth chart) was significantly associated with prolonged duration of stay (p-value<0.001). The

children with shorter hospital stay had less incidence of being moderately and severely undernourished. Stunting (p value < 0.001) and severe wasting (p-value 0.036) were significantly associated with prolonged hospital stay. The incidence of severe wasting was two times higher in those who had prolonged hospitalization. Children who stayed beyond 5 days in the hospital had higher mean number of antibiotic use (2.3±1.4) compared to those with shorter hospitalization (1.3±0.6) (p-value<0.001).

Table 4 shows the association between the variables listed and the duration of hospital stay based on the logistic regression analysis. The following variables were significantly associated with prolonged duration of hospital stay after controlling for other variables: younger age (OR=0.5, 95%CI=0.3 to 0.9, p-value=0.014), low socioeconomic status (OR=2.6, 95%CI=1.4-5.0, p-value=0.003), and number of antibiotics used (OR=3.2, 95%CI=2.2-4.7, p-value<0.001). The other variables (hypoxemia, being underweight, stunted or severely wasted) were not significantly associated with duration of hospital stay based on the multiple logistic regression analysis.

DISCUSSION

The diagnosis of early-onset neonatal sepsis remains to be a challenge to Pneumonia remains as one of the most common infectious diseases affecting the vulnerable pediatric population especially those under five years of age. A child being admitted for severe pneumonia poses a great impact on the resources of his/her family only to be compounded by a prolonged length of stay in the hospital if seen with adverse predictive factors. In our study, younger age was found to be a significant variable contributing to prolonged hospital stay. Children 6 to 11 months of age may have been more susceptible to infections owing to their immature immune system and underdeveloped mechanisms to combat disease as compared to the relatively older age group. This is congruent with the results of the study of Kaiser, S.V. and colleagues in 2015 exploring the risk factors for prolonged length of stay and complications of children less than 18 years old diagnosed with pediatric respiratory diseases inPneumonia remains as one of the most common infectious diseases affecting the vulnerable pediatric population especially those under five years of age. A child being admitted for severe pneumonia poses a great impact on the resources of his/her family only to be compounded by a prolonged length of stay in the hospital if seen with adverse predictive factors. In our study, younger age was found to be a significant variable contributing to prolonged hospital stay. Children 6 to 11 months of age may have been more susceptible to infections owing to their immature immune system and underdeveloped mechanisms to combat disease as compared to the relatively older age group. This is congruent with the results of the study of Kaiser, S.V. and colleagues in 2015 exploring the risk factors for prolonged length of stay and complications of children less than 18 years old diagnosed with pediatric respiratory diseases in general. The risks of both prolonged LOS and complications during LRI

hospitalizations were increased in younger children. In their study, odds of prolonged LOS decreased 2% and complications decreased 5% for every year of age, making the odds of these events up to 85% higher in infants. Possible reasons for this included more severe disease courses in the younger children or greater variation in the care of young children, such as in the use of pulse oximetry in monitoring their course. (6) Furthermore, Pati et al (2012) also found that risks of prolonged LOS were highest in the youngest children admitted for pneumonia. (7) Meanwhile, the results in this study also had contradicting results with the recent study of Mohakud, N.K. et al in 2018 wherein the hospital stay was significantly higher in children diagnosed with lower respiratory tract infections within the age range of 11-14 years in comparison to 1 month to 1-year aged children. However, in their study, other lower respiratory tract infections such as bronchiolitis, wheeze-associated lower respiratory tract infection were included aside from pneumonia. (9)

Other variables such as sex and vaccination status did not yield any significant correlation with prolonged hospitalization. This is like Kuti wherein no statistically significant relationship was found between the duration of hospital stay and variables such as sex and immunization status of the children. In this study, among those children with a prolonged hospital stay, majority were males although no statistical significance was found in this study. This is similar to the findings in the retrospective study of Mohakud et.al in 2018 wherein the duration of hospitalization was found to be higher in males indicating that sex has a role in susceptibility and severity of the disease. The study cited findings in a paper by Muenchhoff M et al stating that there was a stronger humoral and cellular immune response to infection in females than males. (10) Vaccination status also did not have a statistical significance with regard to the duration of hospital stay. In this paper, as high as 86.6% of the children included in the study had incomplete vaccination for age although when all other factors were adjusted, this did not yield any impact on the results.

Having a low socioeconomic status was also found to be significant in relation to the prolonged hospitalization. In this study, there was a higher proportion of low socioeconomic status patients in those who had prolonged hospital stay compared to those with shorter hospital stay. In the study by Kaiser, S.V. et al in 2015, socioeconomic status was also part of the variables studied contributing to prolonged length of stay. In the aforementioned study, most hospitalizations were of children coming from the lower median household income quartiles and those with public insurance as the payment source. Low socioeconomic status had significant correlation with a longer hospital stay. Findings such as these may likely be attributed to multiple factors that may include worse disease severity on presentation which contributed negatively to the course of the patient upon admission. The resource-poor families might have no money to shoulder transportation costs to bring the patient to the hospital hence late presentation and consult. The investigators of the aforementioned study, however,

recommended further research to investigate whether the results were due to differences in processes of care, quality of care, or other outcomes related to inpatient management for children with different insurance coverage.

In this study, only a few patients recorded values more than 70 cycles per minute among the participants in the study. Respiratory rate more than 70 cycles per minute was not significantly related to prolonged hospital stay similar to results in the study of Kuti et. al in 2014. This is also congruent with the findings of Jakhar et al in 2017 wherein respiratory rate more than 70 cycles per minute was not significantly related to longer hospital days among patients with pneumonia between 2 months to 5 years of age.

This study also found out that children who used a greater number of antibiotics had prolonged hospital stay compared to those with fewer antibiotic uses. Those with prolonged hospital stay significantly had higher mean number of antibiotic use compared to those with short duration. Children diagnosed with community acquired pneumonia requiring multiple antibiotic use may signify a more complicated course of the disease. As a result, the duration of antibiotic use may contribute to the prolonged hospital stay of patients especially among the younger age group wherein intravenous antibiotics were preferred more than the oral route of administration especially for those children unable to feed per orem. This may further explain the additional number of days that the patient needed for mere completion of antibiotics alone. Findings were congruent with the study of Tiewsoh et. al in 2009 which explored the factors determining the outcome of children hospitalized with severe pneumonia in India. This prospective study involved 200 children aged 2 months to 5 years of age and the researchers found out that 56.5% of the children enrolled needed a change in the antibiotics and 51% stayed for more than 5 days in the hospital. The need of change of antibiotics was found to be significantly associated with increased hospital stay among the under-five children hospitalized for severe pneumonia. (11)

A prospective cohort study is recommended, among the under-five age group presenting with severe pneumonia to determine other risk factors for prolonged hospitalization to include laboratory parameters and other ancillary diagnostics such as chest x-ray. Similar future studies may also be done focusing on the adolescent age group as well.

Based on the findings presented, variables such as younger age, low socioeconomic status and greater number of antibiotics used were found to be significantly associated with prolonged duration of hospital stay after controlling for other variables. On the other hand, hypoxemia, respiratory rate more than 70 cycles per minute and presence of malnutrition such as being overweight, stunted or wasted did not yield any significant correlation with the longer length of hospital stay among the patients included in the study.

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TABLE 1 SOCIO-DEMOGRAPHIC CHARACTERISTICS OF THE CHILDREN

Parameter	N=320	Percentage (%)
Age range		
6 -11 months	103	32.2%
1-5 years	217	67.8%
Sex		
Male	194	60.6%
Female	126	39.4%
Incomplete vaccination for age	277	86.6%
Low socio-economic status	225	70.3%

TABLE 2 ASSOCIATION BETWEEN SOCIO-DEMOGRAPHIC CHARACTERISTICS AND DURATION OF HOSPITAL STAY

Parameters	Duration of hospital stay > or = 5 days N=132 (41.2%)	Duration of hospital stay <5 days n =188 (58.8%)	Total	X^2	*p*-value
Age range					
6 -11 months	56 (42.4)	47 (25.0)	103	10.8	**0.001**
1-5 years	76 (57.6%)	141 (75.0)	217		
Sex					
Male	81 (61.4%)	113 (60.1)	194	0.05	0.821 (NS)
Female	51 (38.6%)	75 (39.9)	126		
Incomplete vaccination for age	120 (90.9%)	157 (83.5)	277	3.6	0.056 (NS)
Low socioeconomic status	110 (83.3%)	115 (61.2)	225	10.8	**<0.001**

P value significant at <0.05

TABLE 3 ASSOCIATION BETWEEN CLINICAL FEATURES AT PRESENTATION AND DURATION OF HOSPITAL STAY

Parameters	Duration of hospital stay > or = 5 days N=132 (41.2%)	Duration of hospital stay <5 days n =188 (58.8%)	Total	X^2	p-value
Hypoxemia	48 (36.4)	41 (21.8)	89 (27.8)	8.2	**0.004**
RR >70	8 (6.1)	5 (2.7)	13 (4.1)	2.3	0.129 (NS)
Underweight Moderate Severe	 22 (16.7) 32 (24.2)	 27 (14.4) 17 (9.0)	 49 (15.3) 49 (15.3)	 15.4	 **<0.001**
Stunting	65 (49.2)	46 (24.5)	111 (34.7)	21.0	**<0.001**
Severe Wasting	28 (21.2)	19 (10.1)	47 (14.7)	8.5	**0.036**
Number of antibiotics used	2.3±1.4	1.3±0.6	1.8±1.1	t-stat-8.7	**<0.001**

P value significant at <0.05

TABLE 4 ASSOCIATION BETWEEN VARIABLES AND DURATION OF HOSPITAL STAY BASED ON MULTIPLE LOGISTIC REGRESSION ANALYSIS

Parameters	Unadjusted Odds Ratio (95%CI)	P-value (simple logistic regression)	Adjusted Odds Ratio (95%CI)	P-value (multiple logistic regression)
Age 6 -11 months 1-5 years	 0.4 (0.3-0.7)	 0.001	 0.5 (0.3-0.9)	 **0.014**
Low socioeconomic status	3.2 (1.8-5.5)	<0.001	2.6 (1.4-5.0)	**0.003**
Hypoxemia	2.0 (1.2-3.4)	0.005	1.8 (1.0-3.2)	0.059 (NS)
Underweight Moderate Severe	 1.5 (0.8-2.8) 3.5 (1.8-6.6)	 0.202 <0.001	 0.9 (0.4-2.2) 2.1 (0.6-6.8)	 0.816 (NS) 0.223 (NS)
Stunting	3.0 (1.8-4.8)	<0.001	1.8 (0.9-3.6)	0.109 (NS)
Severe Wasting	2.3 (1.2-4.4)	0.008	1.0 (0.4-2.8)	0.960 (NS)
Number of antibiotics used	3.2 (2.3-4.4)	<0.001	3.2 (2.2-4.7)	**<0.001**

CONGENITAL HEART BLOCK SECONDARY TO NEONATAL LUPUS

ROSA MAGENTA C. CAMACLANG

ABSTRACT

Neonatal lupus is a passively acquired autoimmune disease that occurs in children of mothers with anti-Ro/SSA and/or anti-La/SSB antibodies. [1-4] The most serious complication in the neonate is complete heart block. [3-8] This is a case report of a newborn female presenting with persistent bradycardia detected in utero. The diagnosis was confirmed by maternal anti-Ro/SSA and/or anti-La/SSB antibodies and in utero detection of fetal heart block on echocardiogram. Therapeutic management involved placement of a permanent pacemaker.

KEYWORDS: neonatal lupus, congenital heart block, anti-Ro/SSA and/or anti-La/SSB antibodies

INTRODUCTION

Neonatal Lupus Erythematosus (NLE) is an autoimmune-mediated disorder resulting from placental transference of maternal antibodies (anti-Ro/SSA and/or anti-La/SSB) to the fetal circulation. [1-4] Infants with neonatal lupus can present with a clinical spectrum of cutaneous, cardiac, hematologic, and hepatic abnormalities, but the most life-threatening and irreversible manifestation is congenital complete heart block, mostly diagnosed between 16th to 28th weeks AOG presenting as fetal bradycardia. [6,7,9]

Congenital heart block (CHB) refers to any abnormality in the cardiac conduction system that occurs in utero, at birth, or within the first 28 days of life. It is associated with two major etiologies. Anatomical heart defects with developmental abnormalities of the AV conduction tissues are seen in 14-42% of cases. This includes atrioventricular septal defects, levo-transposition of the great arteries, and left atrial isomerism. [3,4] On the other hand, autoimmune CHB represent more than half of the cases and are associated with transplacental exposure to maternal autoimmune antibodies in a structurally normal heart. In the minority of cases, congenital heart block may also be caused by viral infections, drugs, or myocardial ischemic and infiltrative diseases.[4] Immune-mediated congenital heart block is a rare disorder equally affecting males and females, with a global incidence of 1 in 20,000 - 30,000 live births. [3,4] It occurs in 2-5% of pregnancies with positive anti-Ro/SSA and/or anti-La/SSB antibodies, with a 15-20% recurrence rate in subsequent pregnancies. [5,10] Diagnosis of congenital heart block in neonatal lupus is made when fetal heart block is documented in a pregnant mother who is positive for anti-Ro and/or anti-La antibodies. Established autoimmune complete heart block is irreversible, hence most children will require a lifelong pacemaker. Prognosis is generally good following pacemaker insertion, although some may develop heart

failure due to CHB-related dilated cardiomyopathy or left ventricular dysfunction. [3,4,6]

CASE REPORT

This is a case of K.D., a newborn female, who presented with fetal bradycardia. She was born to a 22-year-old gravida 2 para 1 (1011) mother who was cognizant of pregnancy at 8 weeks AOG. The mother had regular prenatal consults with an obstetrician. Ultrasound was done at 12 weeks AOG which showed normal results, with a fetal heart rate (FHR) of 150 beats per minute (bpm). However, fetal Doppler ultrasound at 20 weeks AOG detected fetal bradycardia at 51-53 bpm. Congenital anomaly scan was done which revealed fetal bradycardia and cardiomegaly with left axis deviation. On fetal echocardiogram, the patient had 2:1 atrioventricular block with an atrial rate of 120 bpm and a ventricular rate of 53 bpm.

The mother was then transferred to our institution where she had her prenatal consults starting at 24 weeks AOG. Repeat fetal echocardiogram showed complete atrioventricular block. There was no structural cardiac defect and no evidence of hydrops noted. A referral to Cardiology and Rheumatology service for co-management of the patient was done. Although asymptomatic, the mother was worked up for systemic lupus erythematosus (SLE). She was positive for ANA, anti-dsDNA, anti-Ro/SSA, and anti-La/SSB antibodies and negative for Antiphospholipid Antibody Syndrome (APAS). The mother denied exposure to viral exanthems or radiation. She denied smoking and alcoholic beverage drinking during her pregnancy. There was no history of rheumatologic disorders nor cardiac diseases in the family.

The patient was delivered term, 37 weeks by Ballard Score, via cesarean section secondary to arrest in cervical dilation. She had an APGAR score of 6, 8 and a birth weight of 2.4kg. There was no note of cord coil nor meconium-stained amniotic fluid. Pertinent physical examination at birth showed that the patient was awake, with good cry and good activity. Vital signs showed a normal blood pressure of 70/40 mmHg, bradycardia with a cardiac rate of 53 bpm, normal respiratory rate of 60 cycles per minute and normal temperature of 36.60C. Oxygen saturation was maintained at 93-98% at room air. Anthropometric measurements were normal for age, with a birth length of 51 cm, head circumference of 33 cm, chest circumference of 32 cm, and abdominal circumference of 31 cm. The patient had no episodes of cyanosis or jaundice. She had a normocephalic head with flat fontanelles, no skin rashes or discoloration, and no cleft lip or palate. Chest examination showed symmetric chest expansion, with shallow intercostal retractions and clear breath sounds. She had adynamic precordium, with regular rhythm, and with no appreciable murmurs. Her abdomen was globular, soft with normoactive bowel sounds and without palpable organomegaly. The umbilical cord was inspected and seen with 2 arteries and 1 vein. There was no lumbosacral mass or dimpling noted, and she had patent anus. The extremities were grossly normal, with full non-bounding pulses, warm extremities,

and capillary refill time of less than 2 seconds.

The admitting impression was Full term, 37 weeks by Ballard Score, Appropriate for Gestational Age, Congenital Complete Heart block secondary to Neonatal Lupus. On admission, the patient was hooked to a cardiac monitor and to non-invasive positive pressure ventilation. Complete blood count (CBC) showed thrombocytopenia of 119. Arterial blood gas (ABG) and was normal. Chest Xray showed an inhomogenous opacification of the left hemithorax, which may be secondary to a cardiomegaly or pneumonia. 15-L electrocardiography (ECG) showed bradycardia at 53 bpm and premature ventricular contraction in bigeminy (Fig. 1). Echocardiography showed bradycardia, patent foramen ovale, patent ductus arteriosus, and a normal ejection fraction of 67% (Fig. 2). Routine newborn care was rendered. She was started on dopamine at 5mcg/kg/min with noted increase in the heart rate to 60-90 bpm.

On the third hospital day, the patient had episodes of desaturation and tachypnea at room air. She was bradycardic at 40 bpm while asleep. There was also noted diaphoresis especially during crying. On the fifth hospital day, the patient was bradycardic at 45 bpm even while awake. Dopamine drip was increased to 7 mcg/kg/min but she remained bradycardic at 40-50 bpm. Otherwise, she had good suck and good activity. On the sixth to thirteenth hospital day, the patient still had persistent bradycardia with heart range ranging from 40 to 60 bpm despite inotropic support. The rest of the physical examination was otherwise well, and she was able to tolerate full feeding.

Titration of vasopressors was done; however due to persistent bradycardia, the patient underwent pacemaker insertion on the 14th hospital day. Post-operatively, the patient improved, and the baseline heart rate increased to 90 bpm. She had no episodes of cyanosis, desaturation, nor hypotension. Dopamine drip was discontinued. She was eventually discharged on the 22nd hospital day and is on regular follow-up at the Neonatology and Cardiology clinics.

DISCUSSION

Neonatal lupus (NL) is a passively acquired autoimmune disorder in which maternal autoantibodies to anti-Ro/SSA and/or anti-La/SSB are transplacentally acquired by the fetus. [1-4] It is a clinical entity distinct from systemic lupus erythematosus (SLE), in that most mothers and infants are not affected by the disease per se. In a study done by Brito-Zeron, P. et al, more than 50% of mothers were classified as asymptomatic carriers of anti-Ro and anti-La antibodies.[4] In relation to the patient, her mother was asymptomatic at the time she was tested at 24 weeks AOG and turned out positive for anti-Ro and anti-La antibodies.

The major manifestations of NL are cardiac and cutaneous findings, although hepatic involvement and hematologic abnormalities such as anemia and thrombocytopenia have also been reported. [2,3,6] Congenital heart block is the only

serious and irreversible condition seen in NL, which may manifest as a slow ventricular heart rate in a structurally normal heart.[1,3] Cardiac NL syndrome also includes further cardiac abnormalities such as endocardial fibroelastosis (EFE), dilated cardiomyopathy (DCM), and valve fibrosis.[3] However, in connection with the patient, the only manifestations seen are congenital heart block, diagnosed in utero by fetal echocardiogram and postnatally by electrocardiogram, and thrombocytopenia seen in the first 2 days of life.

The incidence of autoimmune CHB varies between 1 in 20,000 - 30,000 live births in the general population. [2,3,4] In the local setting, congenital heart block occurs in about 1 in 52,000 reported cases in the Philippine Pediatric Society (PPS) Registry.[11] This includes autoimmune, structural heart abnormalities, and other forms of congenital CHB. The Philippine Children's Medical Center only had 3 reported cases of congenital heart block as to date, with no data available on the etiology of the heart block, as well as the incidence of neonatal lupus. [11]

The non-cardiac manifestations usually resolve as maternal antibody levels in the fetal circulation declines, but cardiac damage tends to be irreversible. Atrioventricular block typically develops at 16th to 18th weeks AOG, peaks at 20th to 24th weeks AOG, and most occur before 30 weeks AOG. [12] Exposure of the developing atrioventricular (AV) node to maternal autoantibodies results in local inflammation, calcification, and permanent fibrosis of the fetal AV node, which can block signal conduction at the AV node in an otherwise structurally normal heart. [4,6]

The majority of autoimmune CHB present with type III or complete heart block. This is defined as the absence of AV conduction, with severe reduction in the fetal ventricular heart rate. [4] Since this consequence is irreversible, it carries a high morbidity and mortality rate, especially when diagnosed in utero. The lower the heart rate, the higher the possibility of fetal hydrops, neonatal cardiac failure, and death. [3,8] Nonetheless, this was not the case of the patient. Although she was diagnosed in utero at 24 weeks AOG, she did not manifest with any signs of hydrops or cardiac failure. She was eventually born full term at 37 weeks AOG.

The diagnosis of CHB in neonatal lupus is made when the following are both present: a mother or affected child with anti-Ro/SSA and/or anti-La/SSB antibodies, and heart block detected in utero between 16th to 28th weeks AOG, or in the neonatal period. The timing of diagnosis is related to the peak of transplacental passage of autoantibodies and ontogenic development of cardiac conduction system that is not fully developed until the 22nd week. [3] In reference to the case, the mother initially had normal ultrasound findings at 12 weeks AOG, with an FHR of 150 bpm. However, fetal bradycardia was noted on congenital anomaly scan at 20 weeks AOG, and echocardiogram done 24 weeks AOG documented fetal heart block. This was associated with a mother who was asymptomatic but tested positive for ANA, anti-dsDNA, anti-Ro/SSA and anti-La/SSB

antibodies. Complete heart block was confirmed on postnatal electrocardiogram done on the 1st day of life. These findings are consistent with a diagnosis of congenital heart block secondary to neonatal lupus.

Once heart block is documented in utero, a more intensive monitoring with frequent fetal echocardiographic surveillance is advised for women who test positive for Ro/SSA and La/SSB antibodies since detection of heart block at earlier stages may still improve the outcomes.[5] Many experts advise performing weekly fetal echocardiography starting at 16 weeks through 28 weeks AOG. Treatment with dexamethasone improved incomplete AV block and hydropic changes in CHB but did not reverse established complete heart block. The side effects of treatment with dexamethasone must still be weighed against the absence of established benefits. Beta agonists can increase the fetal heart rate in those with congenital heart block, but its impact on the prevention of morbidity and mortality remain in question.[14] The use of Hydroxychloroquine and/or IVIG at the 14th and 18th week of gestation has also been recommended for the prevention of progression to complete heart block but was not proven effective in reducing the incidence of the disease. [3,13]

Overall, management would still vary depending on the serial echocardiographic findings. For those with 1st or 2nd degree heart block, some authors recommend treatment with dexamethasone daily while most would still prefer expectant management. [3,6,13] With regards to the patient, a 2:1 second degree block was initially detected on fetal echocardiogram. She was managed expectantly, and on her repeat echocardiogram at 24 weeks AOG, complete heart block was noted. Management for this will primarily be expectant. If hydrops fetalis or other signs of fetal distress develop, early delivery and emergency pacing may be needed.[13]

Postnatal management of autoimmune CHB involves supportive treatment for those symptomatic, including administration of inotropes. Pacemaker implantation is recommended for those presenting with significant bradycardia of less than 55 bpm, and those with clinical signs of heart failure or failure to thrive. [3,15] In relation to the patient, she was initially managed with Dopamine. However, due to persistent symptomatic bradycardia and a baseline HR of less than 55 bpm despite the use of inotropes, permanent pacemaker insertion was eventually required. Postoperatively, there was marked improvement of her symptoms. She had a baseline heart rate of 90 bpm, and had no episodes of diaphoresis, hypotension, or desaturation.

An estimated 70% will have a pacemaker inserted by age 5, and 90% will require insertion by adulthood. [6,16] Indications for pacing in autoimmune CHB include symptomatic bradycardia, left ventricular dysfunction, baseline heart rate of less than 55 bpm, or a widened QRS complex. Most of these children will require 2 – 3 pacemakers during childhood, followed by subsequent replacement about every 10 years for life. [6] Though pacemaker insertion is an effective therapy for congenital CHB, complications from this

may still develop. Pediatric patients in general are at a higher risk for pacemaker malfunctions. [7] Dilated cardiomyopathy is a well-known complication of congenital CHB. The probability of developing left ventricular dysfunction and dilated cardiomyopathy over time is 4-18%, especially in those chronically paced.[3] Infections are rare, occurring in 0.5% of new pacemaker implantations and 1% of battery changes, but it may prompt the removal of the whole pacemaker system and implantation of another. [6] Generally, prognosis after pacemaker implantation is good. Most of these children can live an almost normal life, and the possibility of developing SLE or other connective tissue disorders in later life seems to be rare. [3]

A diagnosis in infancy of congenital CHB requiring pacemaker essentially commits a patient to multiple surgical procedures, limitations in daily activities requiring an increase in cardiac demand, and lifelong follow-up for close monitoring to avoid possible complications before they occur.

SUMMARY

The case presented is a newborn female with persistent bradycardia in utero and in the neonatal period. Her mother was asymptomatic but was positive for serum maternal antibodies to anti Ro/SSA and anti La/SSB. Fetal ultrasound and echocardiogram done at 20th and 24th week AOG revealed bradycardia and fetal heart block. At birth, electrocardiogram confirmed the diagnosis of a complete heart block. Due to persistent symptomatic bradycardia despite the use of inotropes, she underwent pacemaker insertion which improved the clinical presentation of the patient. The prognosis following pacemaker implantation is excellent for most, although complications such as heart failure may still occur. Therefore, early pacemaker implantation requires vigilance and close follow-up to detect early complications and intervene when the need arise.

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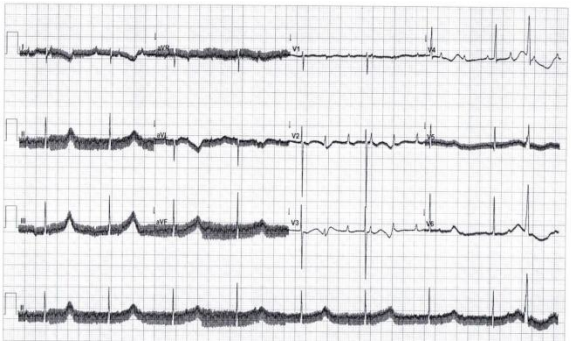

Figure 1. ECG tracing during admission showing fetal bradycardia at 53 bpm

QUANTITATIVE MEASUREMENTS

	PATIENT	NORMAL(cm)		PATIENT(cm)	OTHERS
LA	1.71		IVS (d)	0.38	Ao=
Aorta	0.75		IVS (s)	0.45	PV ann=0.88
LVed	1.64		LVPW(d)	0.47	TV=
LVes	1.08		LVPW(s)	0.45	MV=
RA		RVOT =	Ejection Fraction	67%	DA=0.60
RV		LVOT =	Fractional shortening	34%	RVET=
MPA	1.35	AVA =0.74	RCA proximal=0.14	RCA distal =0.15	LVEF=63%
RPA	0.52	SOV =1.06	LCA main =0.12	LCA distal=0.12	RVEF= %
LPA	0.48	STJ =0.88	LAD =	LCX =	RV FAC=45%
TAPSE		AAO =0.97	VSD =	PDA =0.35	PFO=0.41

COLOR FLOW DOPPLER

Valve	Velocity(m/sec)	Gradient(mmHg)	Orifice Area (cm^2)	Regurgitant Fraction (%)	Others(mmHg)
Mitral	0.74	2.2			MR jet =
Tricuspid	1.04	4.3			TR jet =27
Aorta	1.32	9.4			AR jet =
Pulmonic	1.05	4.4			PR jet =41
Desc. Aorta	1.39	7.7			PE(ant.)=
Qp:Qs =					PE(pos.)=
PAT = 78	PAP=				

FINDINGS:

- Situs solitus
- Levocardia
- Atrioventricular and ventriculo arterial concordance
- PFO measuring 0.41 cm with bidirectional mostly left to right shunting
- Intact interventricular septum
- Mild TR. TR jet of 27 mmHg
- Mild PR. PR jet of 4 mmHg
- Flow acceleration at the ascending aorta with maximum SPG of 9 mmHg across the aortic valve
- Normal chamber dimensions
- Confluent and normal sized branch pulmonary arteries
- Normal coronary artery anatomy
- Normal left ventricular and right ventricular systolic function
- No obstruction to the RVOT and LVOT
- Estimated pulmonary artery pressure by TR jet of 37 mmHg
- Left sided aortic arch
- PDA measuring 0.35 cm with L – R shunting with maximum SPG of 12 mmHg
- No coarctation of aorta
- No pericardial effusion
- Bradycardia noted during examination

FINAL:

PFO
PDA
Mild TR
Mild PR

Figure 2. 2D echocardiography results during admission

TYPICAL CONGENITAL NEMALINE MYOPATHY: ACTA1 PATHOGENIC VARIANT

LEONARDINI A. MESINA

ABSTRACT

Nemaline myopathy (NM) is a primary muscle disorder presenting with proximal muscles weakness at birth or infancy and gross motor delay. This is a case report of a sixteen year old male who presented with proximal muscle weakness at 5 months of age. His gene testing revealed ACTA1 gene mutation, which is associated with nemaline myopathy. He presented with a relatively benign and slowly progressive course of weakness, not complicated by respiratory or cardiac symptoms.

KEYWORDS: *Congenital myopathy, Nemaline myopathy, ACTA1 gene mutation*

INTRODUCTION

Congenital myopathies are a heterogenous group of hereditary primary muscle disorders that are present from birth. These are caused by genetic defects in structural proteins of muscles. Affected individuals usually present with hypotonia, weakness, hypoactive deep tendon reflexes, delayed motor milestones and normal intelligence. Prominent facial weakness and ptosis are present; associated findings include dysmorphic features (dolicocephaly, long, narrow face, high arched palate). The weakness is generalized or more prominent in proximal and limb-girdle muscles; it may be stable or slowly progressive over time. In most severe cases, the presentation is that of a floppy infant with a frog-leg posture and respiratory and bulbar weakness. It has an estimated incidence of around 1:25,00 live births and accounts for 14% of neonatal hypotonia. [1,2] According to the Philippine Pediatric Society (PPS) registry, since 2006, there were only 12 reported cases of congenital myopathies. Of the twelve cases, three were reported in our institution. [3]Nemaline myopathy is the most common form of congenital myopathy. It is characterized by presence of thread or rod-like protein aggregates, called nemaline bodies, which stain dark red with modified trichrome stain within the muscle. [4] This paper presents a case of a sixteen-year-old male, who was diagnosed at our institution as a case of nemaline myopathy. He initially manifested with proximal muscle weakness beginning at 5 months of age.

Case Report

This is the case of a 16-year-old, right-handed, male who presented with weakness of extremities. He was born to a 37-year-old G6P6 (6006) mother, who smoked one pack of cigarette in a day. She denied drinking alcoholic beverages nor use of illicit drugs during pregnancy. She had no maternal illnesses nor comorbidities. The patient was delivered full term via normal spontaneous delivery assisted by an obstetrician in a

tertiary hospital. He had good cry, tone and activity. However, he was admitted for sepsis and treated with intravenous antibiotics for two weeks. He was discharged well and stable.

On his 5th month of life, his mother observed poor head control and floppiness of the extremities. No associated symptoms were noted, such as difficulty of breathing, vomiting, fever, cough, seizures. Consultation with a pediatrician at a tertiary hospital was done. Assessment was undisclosed. No work-up was done. No medications were given, and they were advised to observe his development at that time. In the interim, he had multiple aspiration episodes and recurrent respiratory tract infection with resolution after treatment of prescribed antibiotics. Delay in attainment of gross motor milestones was observed (head control at 6 months, rolls over at 8 months, stands with support at 1 year). Other developmental domains were at par with age. Receptive and expressive language was normal for age; however, his mother noted hypernasality of voice.

At 1 year and 4 months, he can walk alone. However, waddling gait and atrophy of both lower extremities were observed. He would also require assistance when standing from a sitting position. At two years old, atrophy of muscles of upper extremities was noted. Upon consulting a general physician, the patient was assessed as a case of mild cerebral palsy and was advised to undergo physical therapy. Despite weekly physical therapy, interval history revealed persistence of decreased muscle bulk and tone. Due to persistence of symptoms, at the age of five, the patient was brought to our institution for pediatric neurology consult. Based on the clinical findings, he was diagnosed with a lower motor neuron pathology probably myopathy. Electromyography and nerve conduction study (EMG-NCV) was done, which showed neurophysiologic findings suggestive of a myopathic process. Differentials among others include congenital myopathy and muscular dystrophy. Muscle enzyme levels, muscle biopsy and molecular gene testing were advised for definitive diagnosis. Due to financial constraints, these were not performed, and he was again lost-to-follow-up.

In the interim, the patient was able to do activities of daily living without assistance. Proximal muscle weakness persisted. His mother noted difficulty climbing the stairs, brushing his teeth, and combing his hair. Also, he would require support when rising from a sitting position. He was able to go to school, without any learning difficulties. No follow up consult done. At 10 years old, due to persistence of weakness, they opted to consult in our institution. Upon reviewing the patient's family history, no similar clinical features as with the patient were noted. At that time, the patient was ambulatory without assistance, conscious, coherent, not in cardiorespiratory distress. He was also underweight (WFA $z<-2$), not stunted (HFA $z>1$), and severely wasted (BMI $z<-3$). Patient has an elongated face, high-arched palate, with small jaw, and slender built with hips leaning to the right. The rest of physical examination was normal, no chest wall deformities, with clear breath sounds, no murmurs appreciated.

Neurologic examination showed normal mental status; poor masseter tone, weak gag reflex, generalized muscle atrophy, including facial muscles; generalized weakness (MMT 3-4/5); absent deep tendon reflexes; and waddling gait. Sensation and cerebellar function was intact. Signs of autonomic dysfunction, meningeal irritation and Babinski sign were not elicited.

The assessment was myopathy, probably congenital, cannot totally rule out muscle dystrophy. The following were done: (a) repeat EMG-NCV showed progression of previously noted electrophysiologic abnormalities. Findings were likewise suggestive of proximal myopathy with active denervating features; (b) analysis of muscle enzymes revealed mildly elevated results; and (c) dystrophin gene assay was also normal. Thus, muscular dystrophy was less likely and congenital myopathy was highly considered. Muscle biopsy and molecular gene testing were again advised, but not done. The patient was referred to various subspecialty services for a holistic, multi-disciplinary evaluation and care. Patient was referred to Cardiology service. Electrocardiogram and echocardiography were normal. Referral to Pulmonology was also done for evaluation of pulmonary function. Peak flow rate was normal (PFR 82%). Referral to Gastroenterology service for nutritional build-up was also made. He was also referred to Genetics for genetic counselling and Adolescent Medicine for psycho-social support.

Spinal X-ray revealed lateral deviation of spine. Spinal MRI was also done for clearance prior to referral to Rehabilitation Medicine; it showed normal results. Patient was also referred to Pediatric Surgery and was advised to continue physical therapy. Cranial MRI was also done as part of work-up for congenital myopathy due to possibility of subsequent cognitive decline, but with normal findings. On subsequent follow-up, physical therapy resulted to progressive improvement of motor tone. Genetic testing was done. Results showed a pathogenic variant in ACTA1, associated with autosomal dominant and recessive forms of nemaline myopathy. Genetic testing of both parents was done; however, results are still pending.

DISCUSSION

Nemaline myopathy (NM) is the most common form of congenital myopathy. It comprises 17% of cases of congenital myopathies. The term “nemaline”, from the Greek word “*nema*” (rod-like), was coined by Cohen and Shy in 1960s after identifying rod-like structures in muscle biopsies of children presenting with hypotonia. It is characterized by presence of rod/thread-like structures, called nemaline bodies, in the cytoplasm of muscle fibers. [5, 6] According to the National Organization for Rare Disorders, annual incidence is estimated at 1 in 50,000 live births. [7] In the Philippines, however, there is no current local available data stating the exact prevalence of nemaline myopathy. It primarily affects the skeletal muscles, which are voluntary muscles that are used for movements. The signs and symptoms, its severity and age of onset vary greatly in each individual. The cardinal features of nemaline myopathy are weakness and hypotonia, which was observed in our

patient. Muscle weakness is more prominent on the proximal muscles (shoulder, pelvis, upper arms and legs), including the face and neck. [5, 7]

Our patient also presented with an elongated face, high-arched palate, and micrognathia. This characteristic myopathic facies denotes involvement of the facial muscles. Also, our patient presented with a hypernasal voice and multiple aspiration episodes, secondary to involvement of the bulbar muscles. Patients may have a slender built, but muscle bulk is normal. Scoliosis may be present. Although not present in our patient, other deformities include pectus excavatum, abnormal rigidity of spine, or presence of contractures. Involvement of the central nervous system is uncommon; intelligence is normal. Involvement of the respiratory muscles (diaphragm, intercostal muscles) may cause breathing difficulties. The degree of skeletal muscle weakness does not correlate with severity of respiratory muscle involvement. Cardiac muscles are rarely affected. However, in some cases, dilated cardiomyopathy was documented. [5, 7] Involvement of the CNS, respiratory and cardiac muscles were not observed in our patient.

In our case, the patient presented with a slowly progressive floppiness and proximal muscle weakness since his 5th month of life, not complicated by respiratory insufficiency at birth. Based on these, typical (mild) or intermediate congenital NM may be considered. Both would present with a static or slowly progressive course of proximal muscle weakness within the first year of life. No clear distinction exists between these forms. Clinicians are only able to distinguish typical from intermediate form in retrospect. They can only be classified as intermediate congenital NM if weakness prevents them from achieving motor milestones or requires the use of wheelchair and/or ventilatory support at 11 years old. [9] Our sixteen-year-old patient is ambulatory and does not require use of wheelchair nor ventilatory support; this further strengthens the diagnosis of typical (mild) congenital NM. Recent genetic studies have shown that nemaline myopathy may be caused by mutations in at least ten (10) distinct genes (e.g. nebulin (NEB), α-actin (ACTA1), B-tropomyosin (TPM2). Mutation in genes encoding for various structural proteins (more commonly nebulin, α-actin) will cause disruption of orderly organization of sarcomeric proteins and functional interaction between thin and thick filaments during muscle contraction, explaining the molecular mechanism behind the muscle weakness in NM. [10]

A mutation involving the ACTA1 gene, coding for α-actin protein, was detected on our patient's gene testing. Mutation of this gene accounts for 10-20% of cases of NM. Also, more than half of the cases with ACTA1 gene mutation present with severe congenital form of NM, and clinical and radiologic features involving the central nervous system. [11] Interestingly, our patient presented with a benign, slowly progressive course of his muscle weakness, without involvement of the CNS, and supported by a normal craniospinal MRI; thus, making this case worth reporting. The diagnosis of nemaline myopathy can be established histologically with a muscle biopsy and/or

molecularly by gene testing. In this patient, the multigene test panel detected pathogenic variants in ACTA1 gene, one of the genes associated with nemaline myopathy. [5] Since gene testing confirmed the diagnosis of NM in our patient, a muscle biopsy was not done. However, it remains as the gold standard in the diagnosis of NM.

Currently, there is no specific treatment for patients diagnosed with nemaline myopathy. Management is mainly supportive and aimed at controlling specific symptoms present in everyone. Hence, multidisciplinary care in affected individuals greatly impacts the outcome and survival of these patients. [12] Thus, in our patient, a holistic and multidisciplinary approach was undertaken to optimize his quality of life.

After the initial diagnosis is made, disclosure of information and discussion of diagnosis, genetic issues, treatment goals, and family support should be done. Information on prognosis should also be given. Likewise, whether genetic diagnosis is known or not, the risk of recurrence in future pregnancies should be discussed. Specific treatment plans, including preventive health measures and growth and development surveillance, should be enumerated. Lastly, family support and resources should be discussed. [12]

There is currently limited data on the prognosis of patients with nemaline myopathy. However, a research study examined records of patients with nemaline myopathy from Australia and North America. The study concluded that their prognosis is largely dependent on (1) prenatal factors (oligohydramnios, decreased fetal movement) (2) form of NM, (3) presence of severe respiratory insufficiency, and (4) presence of arthrogryposis multiplex. [12] Correlating these, our patient presented with features of typical congenital nemaline myopathy not complicated by severe respiratory insufficiency nor has arthrogryposis multiplex; hence, he has a good prognosis. On follow-up care of patients with NM, frequency of follow-up visits highly depends on the age of onset, severity of symptoms, and organ systems involved. General guidelines recommend that follow up for infants should be every 3 to 4 months; for older children, follow up every 6 to 12 months is standard. Thus, our patient is regularly seen at our institution every 6 months. [13]

In summary, we present a case of a 16-year-old male, manifesting with progressive proximal muscle weakness, with gross motor delay and characteristic facial dysmorphism. Mental status and sensory examination were normal. Gene testing confirmed the diagnosis of nemaline myopathy. Management is mainly supportive, involving a team of competent and committed professionals. There were no signs and symptoms of respiratory insufficiency, cardiac and CNS involvement. Moreover, his clinical course suggests a typical (mild) congenital NM. Therefore, our patient has a good prognosis.

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A CASE OF KAWASAKI DISEASE SHOCK SYNDROME WITH CONCOMITANT *PANTOEA SPP* SEPSIS

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ABSTRACT

Kawasaki disease (KD) is a common systemic vasculitis of childhood involving medium sized arteries that may result in life-threatening coronary artery abnormalities [1]. Children with Kawasaki disease generally do not develop shock however, in some patients a more intense inflammatory response may lead to shock syndrome [2]. This is a case of a seven-year-old male who presented with neck pain, fever, rash, and with clinical signs of poor perfusion and shock. 2D-echocardiography showed dilated coronary arteries, and he was managed as a case of Kawasaki Disease Shock Syndrome (KDSS).

CASE REPORT

K.A.C. is a seven-year-old male who initially presented with unilateral neck pain and came at our institution due to increase in sleeping time. He was apparently well until five days prior to admission when he complained of sudden onset right sided neck pain which was tender to touch. There was no history of trauma or associated symptoms such as fever, cough, colds, headache, or vomiting. No consult was done, and no medications were taken.

Four days prior to admission, there was noted persistence of the right sided neck pain now accompanied by swelling and limitation of movement. He also had fever with a maximum temperature of 39.4oC. He was then brought to a Rural Health Unit and was assessed to have Mumps vs Musculoskeletal Pain. He was given mefenamic acid which provided temporary relief of pain and resolution of fever. Three days prior to admission, there was persistence of symptoms which prompted consult with a private pediatrician. Urinalysis showed pyuria, the assessment was urinary tract infection, for which he was given Cefixime. Two days prior to admission, there was persistence of symptoms now accompanied by erythematous maculopapular rashes on the neck which progressively involved the chest and face. They sought consult with their pediatrician wherein a complete blood count (CBC) was done which showed thrombocytopenia with a platelet count of 146 x 109/L. He was assessed to have dengue fever and was advised CBC monitoring. One day prior to admission, patient had persistence of intermittent fever and right sided neck pain, accompanied by progression of erythematous maculopapular rashes coalescing into plaques now involving the trunk and extremities. There was also erythema and swelling of bilateral hands and drying of the lips. He also had decreased appetite, generalized body weakness, episodes of shortness of breath,

easy fatigability, and occasional non-productive cough. The patient was again seen by his private pediatrician and a complete blood count was done with normal results. He was assessed to have Kawasaki Disease and he was given Cetirizine and Prednisone. On the day of admission, the patient was noted to be drowsy with increase in sleeping time hence consult was done in our institution and was subsequently admitted.

Upon further history, it is noted that the patient usually plays with animals and insects at the mini garden in front of their home, and the patient had a history of thorn pricks within the past month from this admission.

Upon admission, the patient was awake, weak looking, stretcher-borne, and in cardiorespiratory distress. He was hypotensive with a blood pressure of 80/50, tachycardic with a heart rate of 160 beats per minute, tachypneic with a respiratory rate of 35 cycles per minute, afebrile at 37.4oC, and with desaturation at 93% on room air. He had bilateral conjunctival erythema, dry lips, alar flaring, neck stiffness, and swelling of the right lateral neck. Chest examination showed symmetric chest expansion, with noted subcostal and intercostal retractions, clear breath sounds, adynamic precordium, tachycardic, with regular rhythm, and with no murmur. Abdominal examination showed flat abdomen, nondistended, with normoactive bowel sounds, and with direct tenderness over the epigastric area, no organomegaly noted. He had cool extremities, prolonged capillary refill time of 4 seconds, and poor pulses. Upon examination of the skin, there was noted erythematous to hyperpigmented maculopapular rash coalescing into plaques on the trunk and extremities.

The admitting impression was toxic shock syndrome r/o Kawasaki disease, COVID suspect, r/o multisystemic inflammation in children. Fluid resuscitation was initiated accordingly, and vasopressors were started. Blood culture revealed moderate growth of Pantoea spp. He was given appropriate antibiotics, completed Meropenem for 14 days, Amikacin for 7 days, and Vancomycin for 7 days. He was persistently in respiratory distress which eventually led to necessitating ventilatory support and referral to Pediatric Intensive Care. The patient was subsequently referred to the service of Cardiology for 2D-Echocardiogram which revealed dilation of bilateral coronary arteries. He was assessed to have Kawasaki disease shock syndrome hence intravenous immune globulin and Aspirin were initiated. The patient showed significant improvement thereafter and was discharged improved and stable on the 16th hospital day. He came in for follow up check up after 1 week, asymptomatic with reported good appetite and activity. A repeat 2D Echocardiography showed residual bilateral coronary artery aneurysm.

DISCUSSION

Kawasaki disease (KD), formerly known as mucocutaneous lymph node syndrome and infantile polyarteritis nodosa, is an acute febrile illness of childhood seen worldwide, with the highest incidence occurring in Asian children younger than 5

years old [6]. KD in older children is usually prominent among males, with observed delays in diagnosis, presenting with additional signs and symptoms, and a substantial incidence of coronary artery abnormalities [2].

Our patient initially presented with a four-day history of fever associated with right sided neck swelling and pain, erythematous to hyperpigmented maculopapular rash coalescing into plaques, bilateral hand edema and erythema, dry lips, and bilateral conjunctival erythema. He had three of the five principal criteria of Kawasaki disease which are: (1) bilateral nonexudative conjunctival injection with limbal sparing; (2) erythema of the oral and pharyngeal mucosa with strawberry tongue and red, cracked lips; (3) edema (induration) and erythema of the hands and feet; (4) rash of various forms (maculopapular, erythema multiforme, scarlatiniform or less often psoriatic-like, urticarial or micropustular); and (5) nonsuppurative cervical lymphadenopathy, usually unilateral with node size >1.5cm. Also, in KD, fever is characteristically high spiking (> 38oC), remitting, and unresponsive to antipyretics. He also presented with clinical signs of poor perfusion which is rarely seen in Kawasaki disease. He was hypotensive, tachycardic, tachypneic, with poor pulses, prolonged capillary refill time of 4 seconds, and with cool extremities. He also presented with persistent respiratory distress which eventually necessitated ventilatory support. A chest x-ray showed reticulonodular densities and ground glass pneumonic opacities on both lungs. On further work up, laboratories showed: leukocytosis with a white blood cell count of 20.5 x 109/L, thrombocytopenia with a platelet count of 110 x109/L but then developed thrombocytosis with a platelet count of 933 x109/L, elevated inflammatory markers such as C-reactive protein (210.5 mg/L, 21 times elevated), Procalcitonin (36.950 ug/L, 73.9 times elevated), and Erythrocyte sedimentation rate (60 mm/hr, 6 times elevated). With these findings, the patient was admitted and managed as a case of toxic shock syndrome.

KDSS is often misdiagnosed as toxic shock syndrome (TSS) or septic shock as their clinical pictures are similar. Both present with fever, rash, hypotension, multi-system involvement and desquamation. Laboratory studies are then essential to differentiate the two groups. KDSS may present with significantly lower albumin levels indicating a possible correlation between albumin and increased vascular permeability [7]. Thrombocytosis is a characteristic finding in KDSS, whereas thrombocytopenia is more common in other types of shock [3]. The most important difference is the presence of echocardiographic abnormalities, such as valvulitis (mitral or tricuspid regurgitation) and coronary artery lesions in the KDSS group [4].

Another differential diagnosis for this case is the multisystem inflammatory syndrome in children (MIS-C). These findings are consistent with the World Health Organization case definition of MIS-C: (1) age 0-19; (2) fever for □ 3 days; (3) clinical signs of multisystem involvement (rash, bilateral nonpurulent conjunctivitis, or

mucocutaneous inflammation signs, hypotension or shock, cardiac dysfunction, evidence of coagulopathy, acute gastrointestinal symptoms); and (4) elevated markers of inflammation. However, MIS-C was ruled out because our patient had a blood culture growth of Pantoea spp and there was no proven evidence of SARS-CoV-2 infection or exposure.

On further work-up, the blood culture revealed presence of moderate growth of Pantoea spp., hence toxic shock syndrome is more less likely. Pantoea spp is a gram-negative aerobic bacillus that belongs to the family Enterobacteriaceae. It is primarily an environmental and agricultural organism that inhabits plants, soil, and water [9]. Human infections caused by Pantoea spp are most often associated with wound infection with plant material or hospital acquired due to contamination of medical equipment and fluids. The source of these infections is due to thorn pricks, infected parenteral fluids, and indwelling catheters [10]. It commonly results in soft tissue or bone/joint infection and has a predilection for the lungs, with rare cases in pediatric patients of septicemia with respiratory failure [11]. Infections may be life-threatening, especially in young patients with pneumonia. Management mainly depends on antimicrobial susceptibility upon blood culture. In our patient, the sepsis caused by Pantoea spp may just have been an isolated infection but we cannot totally rule out that this could have triggered the Kawasaki disease shock syndrome our patient had.

On the sixth hospital day, the patient was referred to Cardiology for 2D echocardiography. Harada scoring was done with which the patient fulfilled six out of the seven criteria namely: white blood cell count >12,000/mm3 (20.1 x 109/L), platelet count less than 350,000/mm3 (110 x 109/L), C-reactive protein >3+ (210mg/L), hematocrit <35 (31), albumin <3.5 g/dL (2.3g/dL), age <12 years old, and male sex. The patient was then started on intravenous immune globulin. On the eighth hospital day, 2D Echocardiogram was done which revealed bilateral coronary artery aneurysm, hence a confirmed diagnosis of Kawasaki disease shock syndrome. Other cardiovascular findings are myocarditis (50-70%), pericarditis with pericardial effusion (25%), systemic arterial aneurysms (2%), valvular disease, mild aortic root dilatation and myocardial infarcts (1%) [14].

Kawasaki disease shock syndrome is defined as hemodynamic instability during the acute phase of the disease. KDSS is considered a rare disease around the world. The incidence rate of KDSS varied from 2.60%to 6.95% in children in Western countries. In contrast, a study in China reported a lower incidence rate of 1.23% [15]. Kanegaye et al found KDSS in 13 (7%) of 187 KD patients and in the study of Gamez-Gonzalez et al., of 214 patients with KD, 11 (5%) met the definition for KDSS. In our institution, there has been no recorded case of KDSS for the past 20 years. The cause of KDSS is unknown but capillary leakage due to vasculitis, myocardial dysfunction, and cytokine dysregulation are thought to be responsible [16]. The clinical manifestations of KDSS are atypical. It can rapidly develop into shock, and often with strong inflammatory responses which could

lead to coronary artery disease and multiple organ dysfunctions. The patients are hypotensive and would show signs and symptoms of poor perfusion.

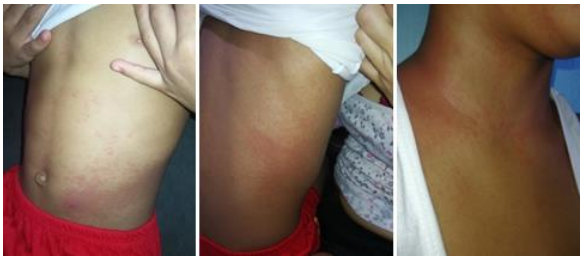
A thorough clinical evaluation of a patient's history and physical examination is the key in establishing the diagnosis of KDSS. No laboratory values are included in the classical diagnostic criteria of KD, but nonetheless may support a diagnosis. Echocardiography should be performed in all patients with KD as soon as diagnosis is suspected to establish a reference point for longitudinal follow-up and treatment efficacy. It is the imaging modality of choice for detection of coronary artery abnormalities and assessment of myocardial function [17]. In addition, initial coronary artery diameter noted on echocardiography is a factor in identifying patients at high risk of developing a coronary artery aneurysm and therefore warranting augmentation of initial intravenous immune globulin therapy. KDSS patients need early aggressive management to reduce systemic and vascular inflammation. The recommended treatment for KDSS includes the use of intravenous immune globulin combined with aspirin and vasoactive drugs. Also, other patients can maintain normal blood pressure by intravenous normal saline. In cases of resistant KD, other therapeutic options would include additional IVIG, corticosteroids, plasmapheresis, methotrexate, tumor necrosis factor inhibitors, cyclosporin and interleukin-1 blockers [19].

The prognosis for most patients with KDSS is excellent. Long term morbidity is primary related to the degree of coronary artery involvement. The rare fatal outcomes from severe cardiac involvement are generally the result of either myocardial infarction or arrhythmias, although aneurysm rupture can also occur. Mistaken or late diagnosis, or complete lack of IVIG treatment, is associated with potentially fatal outcomes [18]. Recurrence rate is low with a reported rate of 6.9 per 10000 person-years with highest incidence in children less than three years of age who had cardiac sequelae during the first episode [20]. Follow up after discharge includes monitoring for recurrence of fever and repeat echocardiograms to assess for cardiac involvement. After the baseline echocardiogram is obtained at diagnosis, echocardiography is usually repeated at approximately two and six weeks of illness to evaluate for coronary involvement [21]. Our patient was seen at the out-patient department after one week from discharge with a repeat 2D Echocardiography showing residual bilateral coronary artery aneurysm.

SUMMARY

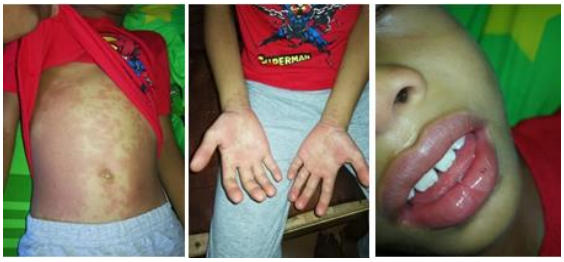
This report presented a seven-year-old male with fever, rash, conjunctival suffusion, edema and erythema of the hands, and right lateral neck swelling. He also presented with signs of respiratory distress and shock. Initially, he was managed as a case of toxic shock syndrome, however this was ruled out due to bacterial growth on blood culture, Pantoea spp. 2D-Echocardiogram showed bilateral coronary artery aneurysm, confirming the diagnosis of Kawasaki disease shock syndrome. Management included appropriate

antibiotics, intravenous fluids, intravenous immune globulin, and aspirin, which all provided notable improvement for this patient. Kawasaki disease shock syndrome is a rare disease recognized worldwide and is commonly misdiagnosed as toxic shock syndrome. The exact cause of KD is still unknown however, it may be triggered by an infection or an inappropriate immune response to an infection. In this case, septicemia caused by Pantoea spp could have provoked a cascade of immune responses ultimately playing a role in the pathogenesis of Kawasaki disease shock syndrome.



A **B** **C**

Figure 1. Image of KAC on Day 3 of Illness with noted appearance of erythematous maculopapular rash on the (a) trunk, (b) back, and (c) neck



A **B** **C**

Figure 2. Image of KAC on Day 4 of illness with (a) progression of maculopapular rash on the trunk now coalescing into plaques, (b) erythema and edema of bilateral hands, and (c) dry lips

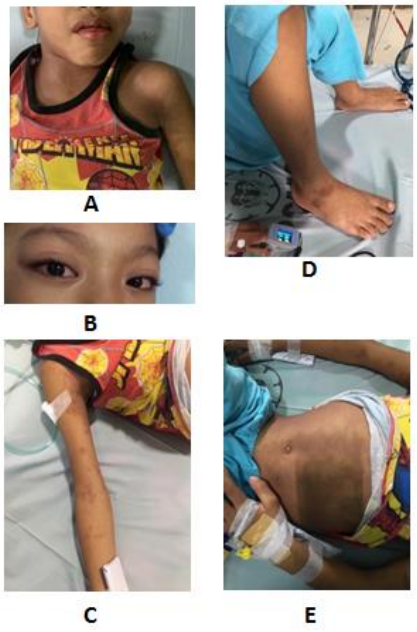


Figure 3. Image of KAC on D5 of illness with noted (a) dry lips, (b) conjunctival suffusion with limbal sparing; progression of the rash involving the (c) upper extremities, (d) lower extremities, and the (e) trunk

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INFANTILE INFLAMMATORY BOWEL DISEASE

MARIA BEATRICE P. TEVES

ABSTRACT

Inflammatory bowel disease is a chronic disorder of the gastrointestinal tract that usually affects adolescents and young adults. It is rare among infants making up only less than 1% of pediatric cases. This is a case of infantile inflammatory bowel disease who presented with early onset hematochezia, with colonoscopy and histopathologic findings consistent with ulcerative colitis. He was managed with mesalazine, a 5-ASA derivative, the mainstay of treatment.

KEYWORDS: Inflammatory bowel disease, Ulcerative Colitis, Infantile Inflammatory Bowel Disease

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, idiopathic, and destructive condition affecting the gastrointestinal tract which encompasses different disease entities namely ulcerative colitis and Crohn's disease. [1, 2] The onset of inflammatory bowel disease is most common during the period of preadolescence, adolescence, and young adulthood. Approximately 25% of IBD cases presents before the age of 20 but may also present in infants as early as first year of life. [3] Infantile and neonatal onset inflammatory bowel disease is extremely rare making up only less than 1% of pediatric cases making this a reportable case. [4]

CASE REPORT

This is a case of a two-year-old male who initially presented with hematochezia at 15 months of age. History started 10 months prior to admission where the patient was noted to have nine episodes of blood streaked yellow to greenish, loose, mucoid stools amounting to ½ cup per episode with no other accompanying symptoms. There was no fever, weight loss or decrease in appetite or activity. Patient was repeatedly managed as a case of amoebiasis and given IV hydration and antibiotics however no response was noted. He was also managed as a case of Cow's Milk Protein Allergy but still with persistence of symptoms. He was referred to a hematologist to rule out blood dyscrasia but work up showed normal results. Consult with a gastroenterologist was then advised. He was seen by a pediatric gastroenterologist and advised admission for work up.

Birth and maternal history were unremarkable. The patient was exclusively breastfed for 4 months and started on mixed feeding thereafter. Complementary feeding was started at 6 months initially with soup, infant cereal products and mashed vegetables. Table food was given starting 8 to 9 months. Currently, he eats four times a day usually consisting of 2 tablespoons of

rice with soup usually with fish, egg and vegetables and consumes 7 ounces of milk every 3 hours. For the past medical history, the patient only had mild pneumonia at 4 months of age with no other known medical illnesses and allergies. There is history of hypertension on the maternal side and no history of inflammatory bowel diseases, cancer, diabetes mellitus, asthma, allergies and blood dyscrasia. Immunization history based on the expanded program on immunization until 1 year old is complete. His development is noted to be at par with age. The personal and social history was likewise unremarkable.

On admission, the patient was seen awake, alert and not in cardiorespiratory distress. Vital signs were within normal limits. Anthropometrics is normal for age. On physical examination, the patient was sallow looking with pale palpebral conjunctivae. The rest of the physical examination including the abdominal examination was normal. The patient was initially managed as a case of Meckel's Diverticulum. Stool exam showed yellowish brown, mucoid, white blood cell count 3-6/hpf, red blood cell count 1-3/hpf with no ova or parasite. Complete blood count showed anemia with low hemoglobin at 63 g/L. WBC was elevated at 28 x 109/L with segmenter predominance at 49%. Patient was hooked to oxygen for support and was transfused with packed red blood cell. A Meckel's diverticulum scan was done but was negative. Colonoscopy showed friable, erythematous, edematous mucosa with scattered areas of whitish exudates from the rectum up to the cecum. Multiple biopsy specimens were taken from the different parts of the colon. Histopathologic findings were consistent with ulcerative colitis showing mild chronic inactive inflammation in the ileum, benign colonic type mucosa with mild chronic active inflammation in the ascending colon, benign colonic type mucosa with moderate chronic active inflammation in the transverse colon and rectum, benign colonic type mucosa with severe chronic active inflammation and reactive glandular changes in the descending colon and benign colonic type mucosa with severe chronic active inflammation and crypt abscess in the sigmoid. No atrophy, dysplasia, crypt distortion or granuloma noted. On further laboratory work up, erythrocyte sedimentation rate was 3.5 times elevated at 35 mm/hr, C-reactive protein was 2.3 times elevated at 26.9 mg/dL and fecal calprotectin showed a positive result. Due to findings consistent with ulcerative colitis and mild disease severity based on the pediatric ulcerative colitis activity index (PUCAI) score of 30, patient was started on mesalazine. On follow up consult after two weeks, patient showed response to treatment by having a decrease in frequency of hematochezia. Based on the pediatric ulcerative colitis activity index, there was a decrease in score from 30 to 20. Plan was to continue mesalazine, to monitor symptoms and to regularly follow up to monitor the patient's disease activity.

DISCUSSION

Inflammatory bowel disease is a complex, multifactorial and lifelong disease which may present in any age group. It is most common among those aged 15 to 29 years old with 25% of cases seen during

childhood and adolescence, and male predominance at all age groups [4,5].

Early onset inflammatory bowel disease (<6 years) constitutes 4 to 10% of pediatric IBD cases while neonatal (< 28 days) or infantile onset (< 2 years) IBD is extremely rare and develops in less than 1% of pediatric patients. [4, 6]. In the Philippines, there are only 30 out of 4,599,665 cases among aged 1-4 years old diagnosed with ulcerative colitis and 8 out 4,601,720 cases among aged 1-4 years old diagnosed with Crohn disease based on data gathered from the Philippine Pediatric Society, Inc. In Philippine Children's Medical Center, there are only 12 reported cases of inflammatory bowel disease, three of which were ulcerative colitis. Of the 12 cases, three were very early onset inflammatory bowel disease and two were infantile onset inflammatory bowel disease. There is no case of neonatal onset inflammatory bowel disease in our institution.

The pathophysiology of inflammatory bowel disease is not clearly understood. It is believed that the development of inflammatory bowel is largely influenced by the interplay between genetics, immune system, microbiome and environment. [3, 5] Children with very early onset inflammatory bowel disease are at higher risk of having a monogenic cause. With over 200 genes associated with inflammatory bowel disease, 52 of these are linked with monogenic diseases often presenting in infancy or those younger than 6 years. The functions of these genes are linked to immune regulation. Presence of genetic mutations result in immune dysregulation leading to disruption of epithelial barrier function, mucosal invasion of bacteria, abnormal immune receptors, increased inflammatory response, disrupted downstream immune signaling and abnormal handling of bacteria resulting in primary immunodeficiency which eventually leads to inflammatory bowel disease. Thus, in patients who present with early onset IBD, further investigation for rare monogenic disorders should be considered especially among those with atypical presentation such as skin problems, frequent infections or dysmorphism. [3, 5] A strong family history is also a risk factor in the development of early onset inflammatory bowel disease. Approximately 44% of children diagnosed with ulcerative colitis under the age of 2 years have a first degree relative with IBD. [3, 5] Aside from genetic causes, environmental factors play a significant role in the disease process. Inflammatory bowel disease may be attributed to improved sanitation and hygiene together with decreased exposure to enteric organisms during early childhood, which is associated to a greater susceptibility to develop an inappropriate immunologic response exposure to new antigens. Moreover, diet and nutrition specifically those rich in processed food, sugar, sweeteners, fats and oil may alter the composition of the normal flora in the intestinal tract or disrupt the intestinal barrier contributing to the disease process. [5,9] Early exposure to antibiotics may interfere in the normal process of developing tolerance to enteric bacteria which may result to inflammatory bowel disease. Vaccination specifically live attenuated

measles vaccine has been linked as a risk factor for development of inflammatory bowel disease. However, evidence is still lacking to confirm this association [3,9] In our patient's case, there was no history of inflammatory bowel disease in the family. Moreover, he did not have any atypical presentation and had no history of recurrent infections making monogenic cause less likely thus not warranting immunology work up. In terms of environmental factors, patient had multiple and early exposure to antibiotic use which may have contributed to the development of his inflammatory bowel disease.

There are many diseases that may mimic the presentation of inflammatory bowel disease. Given the rarity of infantile inflammatory bowel disease, other more common conditions such as allergic and infectious colitis, which were initially considered in our patient, should be part of our differential diagnosis. Primary immunodeficiency states should also be considered especially in patients with early onset inflammatory bowel disease with atypical presentation, recurrent infections and skin or hair manifestations. [3]

Diagnosis of inflammatory bowel disease is based on clinical presentation and is confirmed by endoscopy and histological findings. [5] Expected findings on endoscopy include erythema, edema, loss of vascular pattern, granularity, and friability. [3, 5] An isolated colonic involvement, as seen in our patient, is characteristic of patients with very early onset IBD. [3] On biopsy, chronicity and inflammation that is usually limited to the mucosa is expected. Other histological findings include cryptitis, crypt abscesses, separation of crypts by inflammatory cells, acute inflammatory cells, edema, mucus depletion and branching of crypts. [3] On laboratory studies, they are expected to have anemia, elevated ESR and CRP, elevated WBC count in severe colitis and elevated fecal calprotectin which are all consistent with our patient's laboratory work up. [9]

The goal of treatment in inflammatory bowel disease is to obtain and maintain remission, achieve mucosal healing, and prevention of surgical intervention and development of cancer. [7] Treatment is given to control symptoms and to reduce the risk of recurrence. [3] The recommended first line induction and maintenance therapy for mild to moderate ulcerative colitis is oral 5 – aminosalicyclic acid (5-ASA). [8] It is effective in cases of active ulcerative colitis and in preventing recurrence. [3] Since our patient was considered to have a mild disease activity based on his PUCAI score on admission, he was started on mesalazine, a 5-ASA derivative, which is an anti-inflammatory that works locally on the colonic mucosa and reduces inflammation through a variety of anti-inflammatory processes. It is usually given at 60 to 80 mg/kg/day with a maximum dose of 4.8 grams daily. [8] In patients with moderate to severe disease activity unresponsive to aminosalicylate treatment, corticosteroids are usually given. In severe cases unresponsive to both aminosalicylate and steroids, immunomodulators may be started. Patients with uncontrolled severe disease activity despite 3 to 5 days of intravenous treatment may already require surgical

intervention. The optimal approach is to do total colectomy with endorectal pull-through to maintain continence. Besides medical and surgical management, psychosocial support and counseling especially on diet and lifestyle is important. Processed food and those rich in sugar, sweeteners, fats and oil must be avoided while high intake of dietary fiber is recommended. Close monitoring is recommended especially in early onset inflammatory bowel disease since the risk of developing malignancy begins to increase after 8 to 10 years of disease for about 0.5 – 1% per year. Thus, monitoring every 1-2 years with endoscopy and biopsy is recommended. In cases where significant dysplasia will be detected on biopsy, colectomy may be warranted. [8]

Inflammatory bowel disease is a lifelong condition. It is marked by remissions and exacerbations. [3,5] Early onset IBD has a more severe disease course compared to late onset inflammatory bowel disease as it impacts growth, psychological wellbeing, nutrition, and schooling. [5] Moreover, patients with early onset inflammatory bowel disease are associated with a more aggressive disease course usually refractory to conventional therapies thus requiring greater immunosuppression or in some cases even surgery. [5] In children with ulcerative colitis, most will usually respond to medical management. However, there is a risk of developing colon malignancy secondary to chronic inflammation if not controlled. [8]

In summary, we present a two-year-old male with a 10 month history of lower gastrointestinal bleeding associated with loose mucoid stools, colonoscopy findings of friable, erythematous, edematous, with scattered areas of whitish exudates and histopathologic findings of mild to severe acute to chronic inflammation of the mucosa of the entire colon with crypt abscess in the sigmoid which are all consistent with ulcerative colitis. Having been categorized with mild ulcerative colitis based on the score of 20 to 30 on pediatric ulcerative colitis activity index, he is being managed and maintained on mesalazine, a 5-ASA derivative, which is the first line of treatment for mild to moderate ulcerative colitis. Management does not only warrant medical or surgical interventions. Psychosocial support is also important to promote a good quality of life among these patients.

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