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Arlene Dy-Co, MD
Editor-in-Chief, PIDSP Journal

Correspondence:
Dr. Arlene Dy-Co
Email: pidsp2009@yahoo.com

EDITORIAL

SILVER LINING

This issue celebrates the Silver Anniversary of Pediatric Infectious Disease Society of the Philippines (PIDSP), the owner of this journal. For an organization to endure 25 years and be as relevant in the now as it was at its inception is a feat. To be more relevant and more valuable in its Silver year is an honor.

Silver, 25 years, quarter of a century of staying true to its MISSION AND VISION deserves a pat on the back, an accolade to its pillars and probably a medal for each member but instead our society celebrated this important milestone by giving back… educating our colleagues through various continuing medical education activities. Challenges are never wanting in a span of 25 years, but true to the saying that every cloud has a silver lining this society withstood tests and is always hopeful. How do you measure success? Regardless, success of PIDSP was not handed on a silver platter nor was the society born with a silver spoon. It is with hard work and dedication that each thread was carefully woven to create a tapestry that is a masterpiece seen today.

We have a feature article written by one of the Editorial Board and Secretary of the Society to let you in as to how this Society has been and hopes to be in the future.

Quite early on, our mentors already had the vision that a journal is an important vehicle to communicate, share new information and knowledge and most importantly, to improve pediatric infectious disease practice by publishing sound articles. In this issue, read on a very common disease that presented with a rare manifestation, deep-seated infections like hepatic abscess and infective endocarditis, commonly encountered neonatal sepsis and leptospirosis, and an article on infections in immunocompromised hosts completes our silver anniversary issue.

Silver is always second fiddle to gold, silver medal, silver coin and this only means that we have so much more to achieve, more readers to reach, more topics to explore, and more science to discover.

Cheers to 25 years! And more….

FEATURE ARTICLE

Fatima Gimenez, MD
Editorial Board, PIDSP Journal

Correspondence:
Dr. Fatima Gimenez
Email: timmygimenez@gmail.com

VIBRANT AT 25

The year 2018 marks our Silver Anniversary.

As part of the celebration, we will reintroduce ourselves by way of an article that attempts to embrace who we are. Far from being a mere fact sheet and a chronology of activities and accomplishments, this is a glimpse of our team`s life history.

What is it you know of PIDSP?

The Pediatric Infectious Disease Society of the Philippines (PIDSP) is a non-stock, non-profit subspecialty organization of the Philippine Pediatric Society.

A significant majority of the members are graduates of one of two accredited Pediatric Infectious Diseases fellowship training institutions, namely, the Philippine General Hospital and the Philippine Children`s Medical Center.

What have we done? What are we involved with?

Our Society is recognized as a major player and a voice of influence for pressing childhood concerns in the field of infectious diseases.

The Annual Immunization Calendar, Clinical Practice Guidelines on tuberculosis, dengue, community acquired pneumonia, leptospirosis and bacterial meningitis, antimicrobial use, emerging infections such as SARS, the influenza pandemic, Zika virus and vaccine-preventable diseases and several position papers are noteworthy imprints of our DNA.

Our Society also invests heavily on educational pursuits. Apart from our annual convention, the Society sponsors training workshops, writeshops, module development, medical forums, attendance to regional conferences and provides research and fellowship grants.

On numerous occasions we have successfully collaborated with other organizations for their scientific conferences, helping in educating other doctors and allied health professionals. In the recent years, we were able to cascade several modules on Dengue, HIV and Immunization.

On the aspect of fellowship training, aside from the presence of a Subspecialty Examination Board, we have an Accreditation Committee tasked to formulate and revise operating policies and guidelines and accredit institutions who seek to create fellowship training programs. This is to ensure that the standards set by the Society are met.

Our Society is also actively involved in initiating and participating in medical and vaccine missions. Beneficiaries have included Papa John Inc, a home for street children; He Cares Foundation; and communities affected by Haiyan to name a few.

What is on our bucket list?

The top priority programs include the following: a renewed focus on relevant researches, creation of more scientific modules on diseases of public health importance, dissemination of completed clinical practice guidelines, online continuing medical education (CME) activities and implementation of advocacy programs with both government and non-government agencies.

What keeps us together?

We cannot truly pinpoint one winning ingredient.

The passion for what we do, the mutual respect, the desire to be more and do more for others is part of our culture. This is what keeps us dynamic, relevant and progressive.

ORIGINAL ARTICLE

Profile and Treatment Outcome of Patients with Infective Endocarditis Admitted in a Pediatric Medical Center From 2005-2016

Maribel D. Pasaoa, MD, DPPS, DPIDSP
Ma. Anna P. Bañez, MD, FPPS, FPIDSP

Philippine Children's Medical Center

Correspondence:
Dr. Maribel D. Pasaoa
Email: mabel_pasaoa@yahoo.com.ph

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

ABSTRACT

BACKGROUND: Infective Endocarditis (IE) is an infection of the endocardial surface of the heart. It remains a life threatening infection among extremes of ages and erroneous or late diagnosis may lead to serious consequences.

OBJECTIVE: To determine the clinical profile and treatment outcomes of pediatric patients with IE admitted in a pediatric medical center.

METHODS: This is a retrospective descriptive study on pediatric patients (0-18 years old) diagnosed with IE from January 2005 to June 2016. Patients' medical records that satisfied the criteria for IE based on Modified Duke Criteria were included in the study.

RESULTS: A total of 37 charts were reviewed with male to female ratio of 1:1. Most common chief complaint and physical finding were difficulty of breathing and tachycardia, respectively. Cardiac murmur was appreciated upon diagnosis except in one patient. 70% had ventricular septal defect and 24% had rheumatic heart disease. Most common associated non-cardiac condition was the presence of dental caries, while only 11% had history of previous cardiac surgeries. 2-Dimensional Echocardiography (2D-Echo) showed vegetation in 97.2% and 49% had positive growth in blood culture. Most common isolate was Streptococci. Empiric therapy included penicillin G (84%) with gentamicin (76%). Complications noted were brain infarct, pericarditis and pulmonary embolism. Majority were managed medically, 7 patients (19%) had vegetectomy and 9 (24%) died during hospitalization.

CONCLUSION: IE is a common complication of congenital heart disease. High index of suspicion is warranted for the early management and prevention of morbidity and mortality.

KEYWORDS: *infective endocarditis, congenital heart disease, Streptococci*

INTRODUCTION

Infective Endocarditis (IE) results when microorganisms adhere to the endocardial surface of the heart. This process usually occurs in heart valves, although septal defects and mural surfaces can be affected. Most episodes of endocarditis begin on endocardium that has been altered by congenital defects, previous disease, surgery, or trauma. [1]

Infective Endocarditis is a major problem worldwide especially in developing countries. It remains a life-threatening infection among extremes of ages and erroneous and late diagnosis may lead to serious consequences. Local data on pediatric cases with IE are difficult to obtain, hence, this study was contemplated. Though several international data[5-12] are available, there was only one local data done in 2009.[4]

Before the use of antibiotics, nearly all patients with IE died from uncontrolled infection. The prognosis improved in relation to advances in its diagnosis and particularly as a result of antibiotic treatment.[2]

METHODOLOGY

This is a retrospective descriptive study of pediatric patients diagnosed with IE from January 2005 to June 2016 at the Philippine Children's Medical Center. Patients' medical records were reviewed. Patients who satisfied the criteria for IE based on Modified Duke Criteria (Appendix A) were included in the study. Demographic data, clinical characteristics, admitting impression, physical findings noted, underlying heart diseases, laboratory findings, blood culture results and number of isolates, 2D echo findings, empiric IV antibiotics started, type and reason for shifting the antibiotics, interventions, complications and treatment outcome were reviewed and tabulated.

The database of the Medical Records Section was utilized to identify cases of IE from the period January 2005 to June 2016. Forty-six patients were identified based on a final diagnosis of IE in the charts and broken down as follows: six (6) from 2005, three (3) from 2006, four (4) from 2007, six (6) from 2008, seven (7) from 2009, three (3) each from 2010 and 2011, two (2) from 2012, five (5) from 2013, three (3) from 2014, two (2) from 2015, and two (2) from 2016. Out of the 46 cases, five charts were not retrieved despite efforts to find them by the records section and investigator, hence only 41 cases were considered as potential subjects for the study. However, four (4) cases were excluded in the final determination of subjects due to: two cases were discharged with final diagnoses of Tetralogy of Fallot not in failure, Cavitary TB and Pneumonia, Septic Shock and 2 did not fulfill the age criteria. In total, there were 37 cases that were included in the study after meeting the Modified Duke Criteria for the diagnosis of Infective Endocarditis.

Table 1 Patients Included and Excluded in the Study

Inclusion/Exclusion	No. of Patients (n=46)	Percentage %
Admitted as IE	46	100
Unretrieved charts	5	1
Final diagnosis not IE	2	4.5
Age > 18 years old	2	4.5
Patients included in the study	37	80

Descriptive statistics such as frequency and percentages were utilized in treating the age, sex, socio-economic status and all categorical variables.

Prior to the conduct of the study, permission was obtained from the Institutional Review Board and Ethics Committee (IRB-EC) of the Philippine Children's Medical Center. Patients' identities were kept confidential and the research was done in accordance to Good Clinical Practice (GCP) guidelines.

RESULTS

There was a total of 37 patient charts reviewed, with age ranging from 6 months to 18 years old with patients in the 5-8 years old age group affected the most. All patients fully satisfied the Modified Duke Criteria with a final diagnosis of Infective Endocarditis (Figure 1). Fifty one percent were males and 49% were females, with a male-to-

female ratio of almost 1:1. Most patients (78%) were admitted to the service ward.

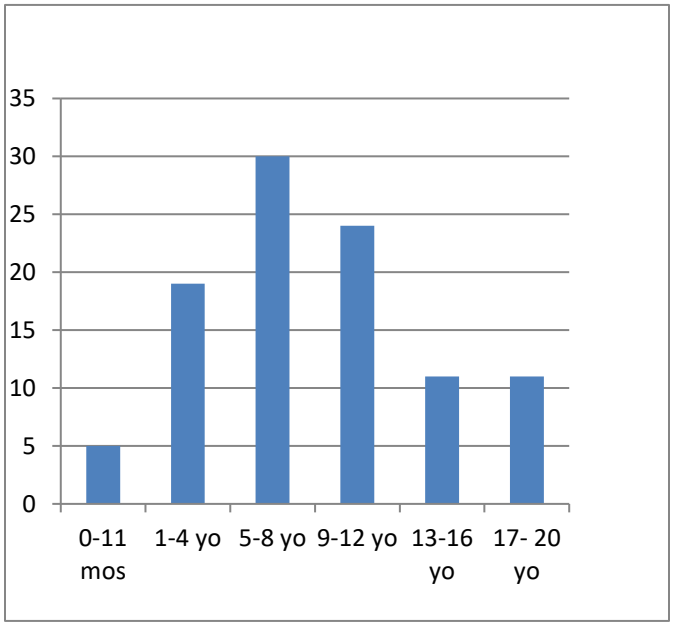

Figure 1. Incidence of Infective Endocarditis by Age Range

CHIEF COMPLAINT

Most of the patients who sought consult had the chief complaint of difficulty of breathing (46%) followed by fever (35%) as reflected on Table 2.

Table No. 2. Distribution of Subjects Based on Chief Complaints

Symptoms	No. of Patients (n= 37)	Percentage (%)
1. Difficulty of breathing	17	46
2. Fever	13	35
3. Headache	1	2.7
4. Weight loss	1	2.7
5. Easy fatigability	1	2.7
6. Cyanosis	1	2.7
7. Pallor	1	2.7
8. Chills	1	2.7
9. Edema	1	2.7

CLINICAL MANIFESTATIONS

Table 3 shows the most common symptoms noted among the patients. The clinical manifestations varied.

Table 3. Distribution of Subjects Based on Common Symptoms

Symptoms	No. of Patients (n = 37)	Percentage (%)
1. Fever	36	97
2. Difficulty of breathing	30	81
3. Anorexia/weight loss	24	65
4. Malaise	22	59
5. Chest pain	18	47
6. Gastrointestinal findings	15	41
7. Cough	15	41
8. Arthralgia	8	22
9. Easy fatigability	8	22
10. Hematuria	7	19
11. Abdominal distention	6	16
12. Orthopnea	6	16
13. Heart failure	6	16
14. Oliguria	5	15
15. Neurologic findings	5	15
16. Headache	3	8
17. Dysuria	1	2.7

The most common symptom was fever (97%) that was present in all but one patient who never had fever all throughout the confinement. Other common manifestations were difficulty of breathing (81%), anorexia and weight loss (65%), malaise (59%), chest pain (47%), coughing and gastrointestinal findings (41%). Dysuria was seen in only one patient.

PHYSICAL FINDINGS

As gleaned from Table 4, tachycardia was the most common physical finding that was noted in all patients. Cardiac murmur was also appreciated in all the patients except for one (97%). Pallor was noted in 59% of patients while hepatomegaly was present in 32% (Table No. 4).

Table 4. Distribution of Subjects Based on Common Physical Findings

Symptoms	No. of Patients (n= 37)	Percentage (%)
1. Tachycardia	37	100
2. Heart murmur	36	97
3. Pallor	22	59
4. Hepatomegaly	12	32
5. Clubbing	3	8
6. Petechiae	2	5
7. Splenomegaly	1	2.7

ADMITTING DIAGNOSIS

Fifty seven percent of patients were managed as IE upon admission. Thirty two percent of patients had underlying cardiac condition but were not diagnosed immediately as case of IE. However, eleven percent of patients were admitted as non-cardiac in origin with one case each of the following diagnoses: Pericardial Effusion secondary to Tuberculosis vs Bacterial pericarditis, Acute Glomerulonephritis Nephritis, Dengue Fever, Fever of Unknown Origin.

UNDERLYING HEART CONDITION

Ninety four percent of patients had underlying heart diseases, 70% of which were congenital heart disease while 24% were cases of rheumatic heart disease. The most common underlying CHD were Ventricular Septal Defect (30%), Double Outlet Right Ventricle (19%) and Patent Ductus Arteriosus (11%). Only two cases were found to have no underlying structural heart condition and were initially admitted as Sepsis (MRSA), Pericardial and Pleural Effusion, t/c IE (MRSA) and Pericardial Effusion secondary to Tuberculosis vs Bacterial Pericarditis. (Table No. 5).

Table 5. Distribution of Subjects Based on Underlying Heart Disease

Heart Disease/Condition	No. of Patients (n= 37)	Percentage (%)
A. Congenital Heart Disease	26	70
1. Ventricular Septal Defect (VSD)	11	30
2. Double Outlet Right Ventricle (DORV)	7	19
3. Patent Ductus Arteriosus	4	11
4. Tetralogy of Fallot (TOF)	2	5.4
5. Coarctation of Aorta (COA)	1	2.7
6. Dilated Cardiomyopathy, severe	1	2.7
B. Acquired		
1. Rheumatic Heart Disease	9	24
C. No structural Heart Disease	2	5.4

ASSOCIATED NON-CARDIAC CONDITIONS

Sixty five percent had associated non-cardiac conditions, the most common of which was dental caries (24%), followed by PTB (11%), pneumonia (8%), malnutrition (8%) and others. (Table No. 6)

Table 6. Distribution of Subjects Based on Associated Non-cardiac Conditions

Non-cardiac Condition	No. of Patients (n = 24)	Percentage (%)
1. Dental Caries	9	24
2. Pulmonary Tuberculosis	4	11
3. Pneumonia	3	8
4. Malnutrition	3	8
5. Skin and Soft Tissue Infection	2	5.4
6. Acute Glomerulonephritis	2	5.4
7. Solitary Kidney with Double Collecting Duct	1	2.7

INITIATING EVENTS TO IE

Seventy six percent had no identified initiating event. Four cases (11%) had previous invasive cardiac intervention including two patients with DORV S/P Pulmonary Artery Band and Bidirectional Glen Shunt, one (1) S/P VSD patch closure and AV valve repair and S/P Embolectomy one month after the initial operation and one patient S/P cardiac catheterization. (Table No. 7)

Table 7. Distribution of Subjects Based on Initiating Events of IE

Initiating Event	No. of Patients (n=37)	Percentage (%)
1. s/p Invasive Cardiac Intervention	4	11
2. Dental extraction	1	2.6
3. ET intubation	1	2.6
4. Unhealed punctured wound	1	2.6
5. Exchange transfusion	1	2.6
6. s/p Central line insertion	1	2.6
7. none	28	75.6

LABORATORY FINDINGS

The following tables and paragraphs show the laboratory findings among the patients in the study.

A. Erythrocyte Sedimentation Rate

Table 8 shows that there was an increase of Erythrocyte Sedimentation Rate among 89% of the patients. While 8% had an ESR within the normal limits.

Table 8. Distribution of Subjects Based on Erythrocyte Sedimentation Rate

Result	No. of Patients (n= 37)	Percentage (%)
1. Increased ESR	33	89
2. Normal Result	3	8
3. Decreased ESR	1	3

B. Complete Blood Count

As shown on table 9, all 37 patients had neutrophilia while 95% had leukocytosis and 84% with anemia.

Table 9. Distribution of Subjects Based on Complete Blood Count Results

Result	No. of Patients (n =37)	Percentage (%)
1. Neutrophilia	37	100
2. Leukocytosis	35	95
3. Anemia	31	84
4. Polycythemia	5	14
5. Thrombocytopenia	3	8
6. Normal	1	2.7
7. Thrombocytosis	1	2.7
8. Leucopoenia	0	0

C. Urinalysis

On urinalysis, hematuria was noted in majority of the patients (73%), followed by pyuria (59%) and bacteriuria (22%). Casts and proteinuria were noted in 8% and 5% of cases respectively. Sixteen percent of the cases had normal urinalysis. (Table No. 10).

Table 10. Distribution of Subjects Based on Urinalysis Result

Result	No. of Patients (n= 37)	Percentage (%)
1. Hematuria	27	73
2. Pyuria	22	59
3. Bacteriuria	8	22
4. Casts	3	8
5. Proteinuria	2	5
6. Glucosuria	0	0
7. Normal	6	16

Two or more blood cultures were done in all patients. 49% of the cases had a positive growth of the same organism in two media while 51% of the cases had no growth (Table No. 11). One case had a growth on pericardial fluid culture.

Table 11. Distribution of Subjects Based on Culture Results

Result	No. of Patients (n =37)	Percentage (%)
1. Positive (+) blood culture	17	46
2. Negative (-) blood culture	19	51
3. P0sitive Pericardial fluid culture	1	2.7

BLOOD /PERICARDIAL FLUID CULTURE ISOLATES

Streptococci (44%) was the most commonly isolated organism, most of which was *Streptococcus mitis* (17%). All of the Streptococcal isolates were sensitive to penicillin. *Staphylococci* were isolated in 22% of cases. There were 2 cases (11%) with *Candida sp*. isolates. There was one case each (5.6%) with *Enterococcus, Kocuria kristinae, Burkholdelia cepacia and Pseudomonas* sp. isolates (Table No. 12).

Table 12. Distribution of Subjects Based on Blood/Pericardial Fluid Culture Isolates and Susceptibilities

Table No. 12: Distribution of Subjects Based on Blood/Pericardial Fluid Culture Isolates and Susceptibilities

Isolate	No. of Patients (n=18)	Percentage (%)	Susceptibility
1. *Streptococci*			
mitis	3	17	Penicillin G
anginosus	1	5.6	Penicillin G
sanguinis	1	5.6	Penicillin G
viridans	1	5.6	Penicillin G
agalactiae	1	5.6	Penicillin G
Streptococcus sp.	1	5.6	Penicillin G
2. *Staphylococci*			
S.aureus			
MRSA	2	11	Vancomycin
MSSA	1	5.6	Oxacillin
S. lentus (MR)	1	5.6	Vancomycin
3. *Enterococcus sp.*	1	5.6	Penicillin G
4. *Candida sp.*	2	11	Amphotericin
5. *B. Cepacia*	1	5.6	Piperacillin-Tazo
6. *Pseudomonas*	1	5.6	Ceftazidime
7. *Kocuria kristinae*	1	5.6	Ampicillin sodium

EMPIRIC ANTIBIOTICS

Majority of the cases were started empirically with intravenous penicillin G (84%) combined with gentamicin (76%) or amikacin (27%). One case was started empirically on vancomycin and gentamicin. This patient had a history of punctured wound two weeks prior to admission. Another case was started on vancomycin and ceftriaxone to cover possible resistant strains of Streptococci (Table No.13).

Table 13. Distribution of Subjects Based on Empiric Antibiotics Used

	Antibiotic Used	No. of Patients (n=37)	Percentage (%)
1.	Aqueous crystalline penicillin G sodium	31	84
2.	Gentamycin sulphate	28	76
3.	Amikacin	10	27
4.	Vancomycin	2	5
5.	Ampicillin sodium	1	2.7
6.	Amphotericin	1	2.7
7.	Ceftriaxone	1	2.7
8.	Piperacillin-Tazobactam	1	2.7

NUMBER OF ANTIBIOTICS USED FOR TREATMENT

There were 21 cases (58 %) that completed treatment with two antibiotics. Among these, 19 cases (90%) were treated with a combination of penicillin plus aminoglycoside, 14 cases (74%) completed 6 weeks of penicillin plus 2 weeks of aminoglycoside with improvement, one case (5%) completed 4 weeks of penicillin plus 2 weeks of aminoglycoside and shifted to oral clindamycin prior to surgery, the other 4 cases (21%) either went home against medical advice (1 case) or died (3 cases) in the course of treatment.

The treatment regimen of the rest of the cases was modified (by switching to different antibiotic/s and/or addition of one more antibiotic/s) either based on culture results or because of lack of clinical improvement and/ or worsening of clinical condition. Seven cases that received multiple antibiotics developed a probable healthcare-associated infection (Table No.13.1).

Table 13.1 Number of Antibiotics Used During the Entire Duration of Treatment

Number of antibiotics used	No. of Patients (n= 37)	Percentage (%)
1	0	0
2	21	58
3	9	24
4	4	10.8
5	1	2.7
>5	2	5.4

DIAGNOSTIC TESTS

The following show the diagnostic results of the patients in the study.

A. Electrocardiographic findings

The electrocardiogram of the patients showed that the most common finding was sinus tachycardia which was seen in 60% of cases while A-V block was noted among 19% of cases (Table No. 14).

Table 14. Distribution of Subjects Based on Electrocardiogram Result

Result	No. of Patients (n = 37)	Percentage (%)
1. Sinus Tachycardia	22	60
2. A-V block	7	19
3. Normal	3	8
4. Atrial fibrillation R axis deviation, LVH	2	5
5. Arrythmias	1	2.7
6. Non-specific ST-T wave change	1	2.7
7. LVH by voltage	1	2.7

B. Initial 2-D Echo Results

Initial 2-D-Echo results showed the presence of vegetation in 97.2 % of cases. (Table No. 15)

Table 15. Distribution of Subjects Based on Initial 2-D Echo Result

Result	No. of Patients (n= 37)	Percentage (%)
1. Positive (+) vegetation	36	97.2
2. Negative (-) vegetation	1	2.7

TIME INTERVAL OF REPEAT 2-D ECHO

As reflected on Table 16, repeat 2-D Echo was done in 92% of the cases. Majority (86%) were done 7-10 days after the start of treatment and at the end of treatment.

Table 16. Distribution of Subjects Based on Time Interval of Repeat 2-D Echo

Time Interval	No. of Patients (n=37)	Percentage (%)
1. 7-10 days after the initial 2-D-echo and at the end of treatment	32	86
2. 5 days from initiation of treatment	1	3
3. 7 days after initial treatment, every two weeks until the end of treatment	1	3
4. No repeat 2-D-echo	3	8

On repeat 2-D-Echo, 15 cases had regression of vegetation, 15 cases had decreased in size and four cases showed no change. (Table No. 17).

Table 17. Distribution of Subjects Based on Repeat 2-D Echo Result

Result	No. of Patients (n=34)	Percentage (%)
1. No noted vegetation	15	44
2. Decreased size of vegetation	15	44
3. Same size of vegetation	4	12

INTERVENTIONS

Majority (67.5%) of the cases were managed medically. There were 13.5% of the cases who had to undergo emergency surgical interventions (Thoracotomy, Thoracentesis, Embolectomy and 2 cases of Pericardiostomy with Biopsy). Nineteen percent of the cases completed medical management prior to discharge with plan for harvesting of vegetation (Table No.18).

Table 18. Distribution of Subjects Based on Intervention Done

Intervention	No. of Patients (n=37)	Percentage (%)
1. Medical management only	25	67.5
2. Medical management, discharged for harvesting at Philippine Heart Center	7	19
3. Medical management and Emergency Surgical Intervention	5	13.5

COMPLICATIONS OF IE

Complications were noted in 43% of the cases, the most common of which was brain infarct or thromboembolic stroke (10.8%) followed by pericarditis and pulmonary embolism both at 5.4% each. (Table No.19)

Table 19. Distribution of Subjects Based on Complications of IE

Complication	No. of Patients (n=37)	Percentage (%)
Cardiac		
1. Pericarditis	2	5.41
2. Cardiac valvular insufficiency	1	2.7
3. Congestive heart failure	1	2.7
4. Collapsed RV wall	1	2.7
Neurologic		
5. Brain infarct	4	10.8
Others		
6. Pulmonary embolism	2	5.41
7. Septic emboli	1	2.7
8. Acute limb ischemia with emboli	1	2.7
9. Glomerulonephritis	1	2.7
10. Myositis	1	2.7
11. Arthritis	1	2.7
12. No complication	21	56.76

PATIENTS' DISPOSITION

Majority of the cases (68%) were discharged with notable improvement. Twenty four percent (24%) of the cases died and 8% of the cases went home against medical advice as shown in Table 20.

Table 20. Distribution of Subjects Based on Patients' Disposition

Disposition	No. of Patients (n=37)	Percentage (%)
1. Discharged	25	68
2. Home Against Medical Advice	3	8
3. Died	9	24

A. Discharged Against Medical Advice

Three patients went home against medical advice. All of them had underlying cardiac diseases (2 VSD and 1 RHD), with associated non-cardiac conditions (acute glomerulonephritis, malnutrition and dental carries) and vegetation. Two patients completed only 5 weeks of antibiotics but had plans to transfer for harvest of vegetation. The third case was previously managed in three different hospitals

before transfer to our medical center. He was unstable on admission and again went home against medical advice after 2 days. Outcome of these three cases, however, were unknown.

B. Mortalities (9 cases)

Nine cases (24%) died in the course of hospitalization. Seven had underlying structural heart disease. Two of the mortalities had no underlying structural heart disease but developed pericarditis in the course of an MRSA bacteremia. Of the 9 mortalities, 3 patients (33%) had previous cardiac surgeries (2 cases of S/P PA Band and Bidirectional Glen Shunt and 1 case of S/P VSD patch closure and AV valve repair). Five cases (56%) underwent emergency surgical intervention: embolectomy, thoracotomy, thoracentesis and 2 cases of pericardiostomy with biopsy. Five cases (56%) had growth in blood cultures: two (2) cases with Staphylococci, two (2) cases with Candida sp. and one (1) case with Streptococcus sp. There was 1 case that grew Staphylococci on pericardial fluid culture but had no growth on blood culture. All cases were noted to have vegetation. Three mortalities had no growth but each case had a complication: one case had septic emboli, one case had brain infarct, and another case had collapsed right ventricular wall with pericarditis.

Table 21. Profile of IE Mortalities

Patient	Underlying Heart Disease	Underlying non-cardiac condition (Surgery Done)	Blood Pericardial Fluid Culture	Vegetation	Complication
1. 5/M	VSD	s/p VSD patch closure and AV valve repair and s/p Embolectomy	*Staphylococcus lentus* (MR)	(+)	Acute Limb ischemia w/ emboli
2. 1F	DORV	s/p PA Band and Bidirectional Glen Shunt s/p Thoracotomy	Candida sp	(+) Tricuspid valve	None
3. 5F	None	Punctured wound 2 weeks PTA s/p Pericardiostomy	MRSA	(+)	Pulmonary embolism
4. 10F	RHD, MR	PTB Malnutrition	*Streptococcus* sp.	(+)	Cardiac valvular insufficiency
5. 7mos/M	Dilated Cardio-myopathy, severe	NICU stay and s/p Intubation 5 months PTA Bronchopneumonia	Candida sp.	(+)	Myositis
6. 5/F	None	TB vs Bacterial Pericarditis s/p Pericardiostomy Pericardial biopsy	Pericardial fluid CS (+) MRSA	(+)	Collapsed RV wall Pericarditis Pericardial effusion
7. 16/F	RHD	s/p Thoracentesis	No growth	(+)	Brain infarct
8. 4mos/M	VSD	s/p Central line insertion 3 months PTA Admitted in 3 different hospital prior to PCMC	No growth	(+)	Septic emboli
9. 15F	RHD	Chronic Pneumonia	No growth	(+)	Thrombo-embolic stroke - brain
Percentage (%)	78	66 (66)	56 (11)	100	89

DISCUSSION

A wide variety of infectious diseases can mimic IE and the challenge in diagnosis is to interpret, weigh and combine diagnostic findings appropriately[1]. The Modified Duke Criteria (Appendix A), which uses a combination of clinical, microbiologic, pathologic and echocardiographic findings is what is used to diagnose IE[1].

This study reviewed the medical records of 37 pediatric patients who fulfilled the Modified Duke Criteria for the diagnosis of Infective Endocarditis. Seventeen cases fulfilled two major criteria while 20 cases satisfied one major criterion coupled with three minor criteria which were usually presence of underlying cardiac anomaly, fever, cardiac, neurologic and/or embolic complications.

Most of the cases belong to the age range of 5-8 years old, while the study by Sabtirul (2009) showed that majority belong to 7-9 and 16-18-year-old with 7 patients each. Similar to the study by Sabtirul (2009), there was no predilection as to sex because the male to female ratio was almost 1:1. But in a study done by Lin, et. al. (2013), there was male preponderance with male to female ratio of 2:1 [4,6]

Seventy eight percent of patients were admitted at the service ward. It could be inferred herein that most of them belong to the lower to average socio-economic class considering the locale of the study is a government-owned and operated public facility. It is not conclusive though that socio-economic status is a predisposing factor of IE since this was not included in the objectives of this study and cases of IE occur in both developed and developing countries.

The annual incidence rate in the United States was between approximately 0.05 and 0.12 cases per 1000 pediatric admissions from 2003 to 2010, without a significant trend.[5] In this study, the annual incidence rate was between 0.19 and 0 .50 per 1000 admission.

Cases of Infective Endocarditis manifest a wide array of symptoms and clinical manifestations. Difficulty of breathing was the most common chief complaint while fever was the most common clinical manifestation. This is similar to what is reported in literature where dyspnea as the most common chief complaint or reason for admission while fever is the most common (96.2%) clinical manifestation among patients diagnosed with IE [1,4,6]

The most common physical findings were tachycardia and murmur. This is in accordance with studies showing that murmur is noted in 90% of IE cases where most patients have underlying heart disease with existing murmurs. [1]

Although pallor ranked as the third most common physical finding it is not considered so in some literatures. Pallor may be secondary to turbulent blood flow but is commonly due to chronic illness or infection. [1]

Splenomegaly is a common manifestation of IE in children that is found frequently in patients with long-standing disease and other evidence of immune system activation. [1] In this study, only one patient was noted with splenomegaly. Hepatomegaly was more common, noted in 32% of patients.

Clubbing was found in 8% of cases as compared to 10 to 20 percent of children with endocarditis reported in literature and this is related to the underlying heart disease. [1]

In this study, petechiae were noted in five percent of cases. This is in contrast to literature where petechiae are reported in approximately one third of patients especially those with long-standing disease. Petechiae are the most common manifestation of embolization to the skin. These lesions are found most commonly on the extremities, oral mucosa, and conjunctivae. [1]

The classic signs of IE (Osler nodes, Janeway lesions and Roth spots) were not seen in any of the cases in this study. These classic signs are related to both immune complex deposition and septic emboli. Janeway lesions are septic emboli consisting of bacteria, neutrophils, necrosis and subcutaneous hemorrhage. Osler nodes are areas of thrombosis and necrosis while Roth spots are retinal hemorrhages with white or pale centers. These classic signs are reported in 3.8% - 5% of cases of IE in children.[1,4,6] We could not explain why these findings were not seen in any these patients.

Most of the cases (95%) in this study had an underlying heart disease. Seventy percent (70%) of cases had a congenital heart disease while 24% of cases had rheumatic heart disease. Majority of the cases with CHD were cases of ventricular septal defect (30%) followed by double outlet right ventricle (19%). This is similar to the study by Sabtirul, et. al. where 92.3% of the patients with IE had an underlying cardiac disease, the most prevalent of which were congenital heart diseases (61.5%). Nine (34.65%) patients had rheumatic heart disease and one of them even had a concomitant VSD. This is expected as the pathophysiologic mechanisms for developing IE in the pediatric population is enhanced in the presence of any cardiac abnormalities.

Two cases (5.4%) did not have any underlying structural cardiac disease. In the study by Lin, et. al. there were 11 patients (22.9%) with IE who were previously healthy and without structural heart disease. The identified risk factors among these patients were a history of dental problems, previous surgical interventions and a history of infected skin/soft tissue infection, but only the latter was the risk factor that was statistically significant. In this study, one of the two cases of IE without known heart disease had an infected wound on the face secondary to fall. This case yielded methicillin-resistant Staphylococcus aureus (MRSA) on blood culture.

Among patients with IE without a previous heart disease but chronically ill, the presence of an indwelling central venous catheter is an important contributory factor. In the study by Lin, there were five patients without known heart disease, but chronically ill, who acquired IE from indwelling venous catheters.[6.] In this study, one case had an

indwelling central venous catheter. The catheter is said to act as a foreign body and presumably cause microscopic damage by abrading endocardial and valve surfaces.[1]

Dental caries was the most common non-cardiac condition seen in 24% of cases, but dental extraction was mentioned only in one case. Various procedures like dental extraction may cause transient bacteremia leading to colonization of what initially may be nonbacterial thrombotic vegetation following endocardial damage.[1] All cases that had dental caries had associated heart condition: 7 cases with CHD and 2 cases with RHD. In the study by Sabtirul, there was only 1 case that had a dental problem while in the study by Lin, there were 7 cases with CHD and 2 cases of non- CHD cases who had dental caries. [4,6]

Non-specific laboratory tests with significant findings included increased ESR, leukocytosis with neutrophilia, hematuria and proteinuria. These non-specific findings are similarly mentioned in literature. [1,4,6] The presence of hematuria and proteinuria are usually secondary to microemboli in the kidneys and may be accompanied by "pyuria," casts, and bacteriuria. [1]

ECG is useful in the evaluation of patients with endocarditis because it can detect arrhythmias and conduction disturbances that complicate the disease.[1] In this study, the most common electrocardiographic finding was sinus tachycardia that was noted in 60% of cases, followed by A-V block in 19% of cases. There were 8% of cases that showed normal tracings.

The most important diagnostic procedure in the diagnosis of IE is the blood culture. Many different microorganisms are capable of causing infective endocarditis in humans. Gram-positive cocci are the etiologic agents in 90 percent of culture positive cases. Streptococci remain to be the bacteria that are most frequently isolated. Similar to the study by Lin, this study also showed that the most commonly isolated organism is Streptococci. However, two European studies showed Staphylococcus aureus as the most common isolate [10,11] similar to the study of Sabtirul.[4]

The percentage of cases caused by Staphylococci and fungi has been increasing during the past two decades.[10,11] In this study, there were four cases of Staphylococci and two cases of Candida endocarditis. Staphylococcal infection is more commonly associated in children with IE who had a history of skin and soft tissue infection but without underlying heart disease.[11] In this study, one case without a structural heart disease had Staphylococcus aureus (MRSA) in the blood following an infected wound on the face. In another case of IE without structural heart disease, methicillin - resistant S. aureus was also isolated from the pericardial fluid. The third case was a case of VSD s/p VSD patch closure and AV valve repair that had *Staphylococcus lentus* on the blood. All these three cases with methicillin-resistant staphylococcal isolates died. In the study by Lin, among seventeen patients with IE without heart disease, S. aureus was isolated in 5 cases (29.4%), two of which were MRSA.

There was one case of IE who had a growth of Enterococcus. This was a patient with DORV, who was noted to have vegetation and subsequently developed brain infarct. Enterococcal endocarditis is less common in children as compared to adults, accounting for about 4% of cases only.[1]

Kocuria kristinae is a gram-positive opportunistic organism that is rarely isolated from clinical specimen.[12] It was isolated in a patient with VSD who had dental caries, with vegetation on 2D-echocardiogram.

The patient with Enterococcus was treated medically while the patient with *Kocuria kristinae* was referred for vegetectomy after completion of 6 weeks penicillin G and gentamicin.

This study also included two cases of Candida endocarditis. The first case was a case of DORV, s/p PA band bidirectional Glen shunt, s/p thoracotomy. The second case was a post-intubation chronic neonatal ICU patient with dilated cardiomyopathy. Both were given antifungal

(Amphotericin) but died. There were five cases of Candida endocarditis in the study by Lin, three cases of which had CHD while two cases had no heart disease.[6] Most cases of fungal endocarditis in children are reported following cardiovascular surgery and prolonged IV antibiotic therapy.[1]

Although gram-negative bacteria causes 4-5 % of cases of IE in children, the percentage of children with gram-negative enteric bacteremia in whom endocarditis develops is considered low.[1] In this study, there were two cases with (5.4%) gram-negative bacteria namely, *Burkholderia. cepacia and Pseudomonas sp.* Both were patients with RHD with vegetations on 2D-echocardiography. One was discharged after completion of antibiotics while the other one was discharged per request but referred for surgical intervention.

Whenever IE is suspected, 2 or more blood cultures should be done to increase the yield of isolating an organism. In this study, forty six percent (46%) of cases had growth of the same organism in two media while 54% of cases had no growth. The study by Lin, et. al. had a high yield of positive culture (93.8%), while the study of Sabtirul showed only a 23% positive culture.[4,6]

Echocardiography has become a valuable adjunct to the diagnosis and treatment of endocarditis in children.[1] In this study, 2 D-echocardiography showed the presence of vegetations in almost all cases (97%). In the study of Sabtirul, et. al., all patients had vegetations. And in the study by Lin, 66.7% (32) of cases had vegetation. The only afebrile patient was admitted due to severe difficulty of breathing. Echocardiography revealed mitral and tricuspid regurgitation, pericardial effusion with flagellation and collapse of right ventricular wall. Pericardial fluid grew COPS while blood culture was negative but still fulfilling criteria for IE. (Appendix A).

On repeat echocardiography, 44% of cases (15) showed resolution of vegetation while another 44% of cases (15) showed a decrease in size. There were two cases that showed an increase in size on repeat 2-D echo four weeks after the initial treatment. The antibiotics were shifted in one case while the other case went home against medical advice. In the study by Sabtirul, repeat echocardiography after the initial two weeks of antibiotics showed regression in 76 % of cases (13) while increased in size of vegetation were noted in 24% of cases. [4] Serial evaluation to monitor size of vegetation cannot assess efficacy of antibiotic therapy as decrease in size or disappearance of vegetation may take a while even after completion of treatment.[1]

In the pre-antibiotic era, infective endocarditis was a uniformly fatal disease.[1] Antibiotic combinations produce a rapid bactericidal effect through synergism, and this was applied in all cases in this study. In this study, majority of the cases (84%) were treated empirically with penicillin and an aminoglycoside. This is similar to the study by Sabtirul where most of the cases (73.1%) were also started empirically with the same combination. The combination of penicillin and aminoglycoside in this study turned out to be an appropriate empiric regimen as Streptococci was the most common isolate. Empiric coverage for *Staphylococcus aureus* including methicillin-resistant strains should likewise be considered among patients with IE without underlying structural heart disease as Staphylococci is considered an important pathogen in literature among this group of patients as was noted in two cases in this study.

The treatment regimen of the rest of the cases was modified (by switching to different antibiotic/s and/or addition of one or more antibiotc/s) either based on culture results, or because of lack of clinical improvement and/or worsening of clinical condition.

A prolonged course of therapy (at least 4 weeks and often 4-8 weeks) has been recommended as organisms are said to be attached deeply within the fibrin-platelet matrix and exist in very high concentrations with relatively low rates of bacterial metabolism and cell division. This results in decreased susceptibility to β-lactam and other cell wall–active antibiotic drugs.[12] This

recommendation was applied in all the cases in this study.

Surgery has become a valuable adjunct to medical therapy in the management of IE. The general trend has been for surgical intervention to be undertaken earlier and more frequently to prevent complications of endocarditis and lower mortality.[1] Echocardiographic features suggesting a possible need for surgical intervention have something to do with the vegetation, presence of valvular dysfunction and/or perivalvular extension. Surgical intervention is usually indicated if vegetations are persistent after systemic embolization, if there is anterior mitral valve leaflet vegetation, more than 10mm, if there is an embolic event during first 2 weeks of therapy or an increase in vegetation size after 4 weeks of therapy.[1] But the most common reasons for surgical management of IE are CHF, progressive valve dysfunction and embolic phenomena.[12] In this study, 67.5% of patients responded to medical management but 19% had to be transferred for surgical intervention. However, the exact reason/s for surgical intervention and whether these patients underwent the surgical procedure could not be established from the charts. Likewise, the mortalities were not evaluated if they could have benefitted from surgical intervention or not.

There are complications associated with IE that are related to hemodynamic changes caused by local infection and the occurrence of embolization and metastatic infection.[1] Cardiac and neurologic were the most common complications noted in this study occurring in 14% and 11%, respectively. However, in the study of Sabtirul, glomerulonephritis was the most common complication in 58% of cases followed by neurologic sequelae (27%)[4] The presence of complications may also worsen the prognosis.[1] In this study, 89% of those cases with a complication died.

With the current improved methods of diagnosis and therapy, 80 to 90 percent of children with this disease can be expected to survive [1] in this study, 76% of cases survived.

RECOMMENDATION

This study yielded only 37 charts in 10 years, hence, a multi- center chart review or registry is recommended to increase the study population and allow statistical analysis of data. This will enable identification of risk factors for IE especially among patients without structural heart defects that are more difficult to recognize. Likewise, statistical analysis will identify risk factors for severe disease or mortality that may help improve its outcome.

APPENDIX A

Modified Duke Criteria for the Diagnosis of Infective Endocarditis (IE) 1-4

Major Criteria
1. Positive blood culture for IE A. Typical microorganism consistent with IE from 2 separate blood cultures as noted below: (i) viridians streptococci, Streptococcus bovis, or HACEK group (ii) community-acquired Staphylococcus aureus or enterococci, in the absence of a primary focus
B. Microorganisms consistent with IE from persistently positive blood cultures defines as (i) > 2 positive blood cultures drawn >12 hours apart or (ii) All of 3 or a majority of > 4 separate blood cultures (with first and last sample drawn > 1 hour apart) 2. Evidence of endocardial involvement A. Positive echocardiogram for IE defined as: (i) oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, or (ii) abscess, or (iii) new partial dehiscence of prosthetic valve, or

C. New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)
Minor Criteria:
1. Predisposition: predisposing heart condition or intravenous drug use
2. Fever: temperature > 38.0C
3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
4. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth spots and rheumatoid factor
5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE
6. Echocardiographic findings: consistent with IE but do not meet a major criterion as noted above
Clinical Criteria of Definite IE:
2 major criteria, or
1 major and 3 minor criteria, or
5 minor criteria

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ORIGINAL ARTICLE

CLINICAL PROFILE AND FACTORS AFFECTING OUTCOME OF FILIPINO CHILDREN WITH HEPATIC ABSCESS: 19 YEAR STUDY

Adrienne Michelle B. Lu, MD*
Maria Estela R. Nolasco, MD*
Marilou G. Tan, MD*

*Philippine Children's Medical Center

Correspondence:
Dr. Adrienne Michelle B. Lu
Email: amblumd@yahoo.com

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

ABSTRACT

Objectives: To describe the clinical profile of children with hepatic abscess, determine their laboratory & imaging findings, medical and surgical treatments and study factors affecting its outcome.

Methodology: A retrospective cohort study done in December 2016 on children 0 to <19 years old with a diagnosis of hepatic abscess on imaging from 1997-2015. Demographic, clinical and diagnostic data were correlated with the outcome and presence of complications.

Results: Thirty cases were identified in 19 years but only 25 charts were available for review. Mean age in years was 5.27 +/- 4.80 SD with male predominance. Fever (96%) and abdominal pain (60%) were common symptoms. Only 9 patients had hepatic abscess culture with Staphylococcus aureus (56%) as the most frequent growth. Anemia (76%) and leukocytosis (96%), and solitary (76%), large abscess >5 cms (60%) involving the right lobe (72%), were the common diagnostic findings. Most were treated with antibiotics alone (60%). All patients improved with no mortality noted, while pleural effusion was seen in 8 out of 12 patients with complications. Only male gender was significantly associated with complications both on chi-square (p 0.004) and logistic regression (p 0.008).

Conclusion: Hepatic abscess is a liver infection usually seen among young and male population, manifesting as fever with anemia and leucocytosis. Most were complicated by pleural effusion with no deaths reported. Male gender had significant association with complications.

KEYWORDS: *hepatic/liver abscess, Staphylococcus aureus, deep-seated infection*

INTRODUCTION

Hepatic abscess is an encapsulated collection of suppurative material within the liver parenchyma resulting from bacterial, fungal or parasitic microorganisms[1]. Children have a unique set of predisposing causes for hepatic abscess that include parasitic and skin infections, genetic conditions, malnutrition, abdominal infections and trauma[2]. Although its prevalence is higher among adults than children, this pathology is relevant because of its associated mortality, which ranges from 2 to 12% [3]. Because hepatic abscess presents with nonspecific symptoms, it can be quite difficult to diagnose in a timely manner[1].

There are limited studies on the prevalence of hepatic abscess among children. In India, Chaubey, et al reported 32 cases of liver abscess in children over 5 years[4]. Meanwhile, in Saudi Arabia, 18 cases have been reported by Salahi et al in 10 years[5], and Ba et al described 26 cases over 5 years[6] in Senegal. In our country, the latest data by Baclayon, et al in 1995, reported 45 pediatric cases in a 7-year period following a report of 87 combined cases of adult and children from the Philippine General Hospital between 1985-1991 by Manalo, et al[7]. On the other hand, the Philippine Society of Pediatrics registered about 80 cases of hepatic abscess, specifically amoebic in origin, out of 4,200,445 cases from 1997 to 2015[8].

Availability of local data on pediatric hepatic abscess is limited, thus this paper aims to describe the profile of Filipino children diagnosed with hepatic abscess, and establish possible factors affecting their outcome. Information on their demographics, clinical presentation, diagnostic, laboratory characteristics and microbial etiology will enable us to possibly develop a more systematic approach to its diagnosis leading to an early and appropriate management, proper allocation of medical resources and anticipation of outcomes and possible complications that may warrant aggressive monitoring and management.

OPERATIONAL DEFINITIONS

Hepatic abscess – clinical findings of fever, abdominal pain or right upper quadrant mass supported by findings of abscess on ultrasonography or computed tomography (CT) scan, which may or may not be bacteriologically confirmed.

Comorbid factors / condition – any previous or newly diagnosed illness, or any identified conditions that could have incited the development of hepatic abscess like immunocompromised state, diabetes mellitus, cancer, postsurgical, history of skin/parasitic infection, post trauma and others.

Clinical manifestations – clinical symptoms of patients with hepatic abscess prior to admission

Time to diagnosis – the time from the patient's first clinical manifestation to the time a diagnosis by Ultrasound or CT Scan was established

Time to resolution of symptoms – the time from the initiation of treatment to the resolution of the initial presenting symptom such as fever, abdominal mass or abdominal pain

Complications – development of pleural/pericardial effusion, basilar infiltrates, concomitant or extension of abscess in adjacent or distant sites, hepatopulmonary/ hepatobronchial fistula, rupture, peritonitis, perforation of hollow viscus, ascites, sepsis/septic shock, with or without improvement and others.

Outcome

Cured – disappearance of symptoms with resolution of abscess on repeat imaging

Improved – disappearance of symptoms with no complete resolution or without progression of abscess on repeat imaging

Mortality – resulting in death

Anemia – as defined by the World Health Organization hemoglobin concentration by age[9]

Nutritional status – following the classification in the World Health Organization growth chart

Liver function tests:

Prolonged prothrombin time – >2 seconds from the control[10]

Elevated SGPT/ ALT- 3x the upper limit of normal[11]

Elevated alkaline phosphatase from the upper limit of normal[11]

Elevated ESR - > 20 mm/hr[11]

Cholestasis – direct bilirubin more than 20% of the total if the total bilirubin is >5mg/dL, or direct bilirubin more 1 mg/dL if total bilirubin is less than 5mg/dL[12]

MATERIALS AND METHODS

This is a retrospective cohort study done among all children 0 to less than 19 years old diagnosed with hepatic abscess by either ultrasonography or CT scan admitted in a tertiary medical center from January 1997 to December 2015.

Study Procedure

Convenience sampling or non-probability sampling was done through the records section database wherein charts of all admitted children diagnosed with hepatic abscess were reviewed. The data collection form was submitted to the Ethics Review Board of our institution prior to the conduct of the study. Confidentiality of the records was observed all throughout the research period. The principal investigator had no conflict of interest in doing the study.

Data Processing and Data Analysis

Descriptive data as means with standard deviations (SDs) was used for continuous data and as percentages for categorical data. The demographic, clinical, diagnostic imaging, microbiological, laboratory values and treatment done were analyzed in association with the presence of complications and outcomes. Statistically significant independent factors by univariate analyses were analyzed using logistic regression model. Prognostic factors independently related to mortality or complications were identified with odds ratios (ORs) and their 95% confidence intervals (CIs). Statistical software used in processing the data was Stata Statistical Software: Release 14 (StataCorp. 2015. College Station, TX: StataCorp LP)

Data Collection and Outcome

The principal investigator reviewed all the charts of patients with hepatic abscess wherein the following variables were obtained. Age, stratified into infancy, childhood and adolescent as follows: 0-2 years old, 3-9 years old, 10-18 years old; gender as to either male or female; nutritional status as either severe, moderate or no malnutrition, overweight or obese; co-morbid conditions as to presence of trauma, parasitism, skin lesions, chronic conditions and others; clinical manifestations as to the presence of fever, abdominal pain, abdominal mass, jaundice, vomiting, diarrhea and others; time to diagnosis; time to resolution of symptoms. Laboratory tests done and results (Hemoglobin, WBC, Prothrombin time, Alanine aminotransferase, Alkaline phosphatase, Bilirubin, ESR) as well as microbiologic isolates (hepatic abscess culture and blood culture) were noted. Ultrasound and/or CT scan findings were classified as to size, lobe involvement and number of abscess. Treatment management was described as either using medical therapy alone with what antibiotics or medical therapy with surgical intervention. The length of hospital stay, presence of rupture, pleural effusion, extension, fistula, peritonitis, perforation as complications, as well as the patients' outcome as either improved, cured or died were likewise noted.

The association between these mentioned variables with complications and outcome were analyzed.

RESULTS

Demographic and Clinical Profile

There were 30 patients admitted from January 1997-December 2015 with a diagnosis of hepatic/ liver abscess by imaging. However, only 25 charts were available for review. Efforts to retrieve all 30 charts were done however the records section was not able to provide the complete files. Forty percent (10/25) of patients belonged to the 3-9 years age group (Table 1). Mean age in years was 5.27 +/- 4.80 SD. There was predominance of male subjects at 60% (15/25) with a male to female ratio of 1.5:1. Malnutrition was noted in 56% (14/25) of patients. There were co-morbid conditions in 24% (6/25) of subjects, the most common of which was intestinal parasitism in 67% (4/6), followed by pulmonary tuberculosis in 33% (2/6), and skin lesion (gluteal abscess) in 17% (1/6). Mean time to diagnosis was 22 days (range: 4-120 days) and the mean time for symptom resolution was 34 days (range: 4-122 days). The rest of the clinico-demographic profile is listed in Table 1.

Clinical Manifestations

The most common manifestation was fever, as seen in 24 patients (96%), followed by abdominal pain seen in 15 patients (60%). The one patient who did not present with fever was a one month old, severely malnourished infant with a right upper quadrant mass. Among patients with fever, about 63% (15/24) had one associated symptom other than fever, while 25% (6/24) had two or more associated symptoms with fever. Only 12% (3/24) had fever as the only manifestation. Two (8%) had cough and 2 (8%) other patients had difficulty of breathing, all of them had complications of pleural effusion. There was one patient (4%) who developed diarrhea characterized as loose to watery, non-bloody and non-mucoid with the no note of amoeba or parasites on stool exam.

TABLE 1: CLINICO-DEMOGRAPHIC PROFILE OF SUBJECT PARTICIPANTS

DEMOGRAPHIC / CLINICAL PROFILE	TOTAL N= 25
Age	
0-2 years old	9 (36%)
3-9 years old	10 (40%)
10-18 years old	6 (24%)
Gender	
Male	15 (60%)
Female	10 (40%)
Comorbid condition	
Present	6 (24%)
Absent	19 (76%)
Nutritional status	
Normal	10 (40%)
Moderate Malnutrition	7 (28%)
Severe Malnutrition	7 (28%)
Obese	1 (4%)

Laboratory tests

Anemia[9] was seen in 76% of patients (19/25) with a median hemoglobin level of 96 g/L (range 39 -135 g/L). Ninety six percent of patients (24/25) had leukocytosis having a median white cell count of 19.35 x 10^9/L (range 10 - 44.9 x 10^9/L). Prothrombin time was done in 20 patients (80%) only, with 8 of them (40%) having prolonged results[10]. Alanine aminotransferase levels were determined in 19 patients (76%) with only one (5%) elevated result (3x the upper limit)[11]. Out of 9 patients (36%) with alkaline phosphatase level, only one (11%) was increased (2.7x the upper limit)[11]. There were 9 patients (36%) who had total bilirubin levels of < 5 mg/dl, two (22%) of which were cholestatic[12], with no visible icterisia nor jaundice. Erythrocyte sedimentation rate (ESR) was done in 7 patients (28%) with 6 of them showing elevated results[11].

Microbiologic tests

Blood culture and hepatic abscess cultures were done in 76% (19/25) and 36% (9/25) of cases, respectively. Twenty one percent (4/19) had positive growth on blood cultures only while 56% (5/9) yielded positive growth on hepatic abscess cultures, all of which were *Staphylococcus aureus* isolates (Table 2). No tests were done in any of them to confirm an amoebic cause for the abscesses.

Imaging

Ultrasound alone was done in 36% (9/25) of patients while both ultrasound and CT scan imaging were done in 64% (16/25) of patients which showed the same characteristics of hepatic abscess. The most commonly seen features were abscess size of > 5 cms in 60% of cases (15/25), solitary abscess in 76% (19/25), with 72% (18/25) involving the right hepatic lobe.

TABLE 2: MICROBIOLOGIC TESTS AND RESULTS

Microbiologic tests	Results (n/%)
Blood culture done	19 (76%)
Positive growth	4 (21%)
- *Klebsiella pneumoniae*	1 (25%)
- *Burkholderia cepacea*	1 (25%)
- *Enterobacter aerogenes*	1 (25%)
- *Serratia marcescens*	1 (25%)
No growth	15 (79%)
Not done	6 (24%)
Hepatic abscess culture done	9 (36%)
Positive growth	5 (56%)
- Methicillin resistant *Staphylococcus aureus* (MRSA)	2 (40%)
- Coagulase positive *Staphylococcus aureus* (COPS)	3 (60%)
No growth	4 (44%)
Not done	16 (64%)

Complications

Complications arising from hepatic abscess were observed in 12 patients (48%), most commonly pleural effusion, as seen in 8 (67%) patients, followed by extension in contiguous areas in 4 (33%) patients. Other less common complications were peritonitis noted in 3 (25%) cases and rupture of abscess in 2 cases (17%).

Treatment

All patients were empirically started on broad spectrum intravenous antibiotics upon diagnosis of hepatic abscess. Seventy two percent of cases (18/25) used the antiprotozoal metronidazole in combination with antibiotics such

as oxacillin (40%), gentamicin (32%), third generation cephalosporin (25%) and/or ampicillin (16%). Antibiotics were changed when no clinical improvement was seen, upon worsening of the patients' conditions and/or according to the sensitivities of organisms cultured, usually to vancomycin (33%), piperacillin-tazobactam (33%) or clindamycin (33%). Clindamycin (43%) was the usual stepdown oral antibiotic on discharge, followed by ciprofloxacin (33%) and cloxacillin (24%), with or without metronidazole.

Sixty percent (15/25) of patients were treated with antibiotics alone while 40% (10/25) used antibiotics and surgical decompression. Only 47% (7/15) among those who had large abscess size > 5 cms were managed surgically with antibiotics, while the remaining 53% (8/15) were treated with antibiotics alone. Open drainage was the surgical technique employed in 57% (4/7) of those with abscess size of > 5 cms, while 67% (2/3) of hepatic abscess size $\leq$ 5 cms were drained percutaneously.

Among patients who were given antibiotics alone, 73% (11/15) stayed in the hospital for less than 1 month, while 27% (4/15) stayed for more than a month. Among patients managed medically and surgically, only 20% (2/10) stayed for more than a month while 80% (8/10) were discharged within a month or less.

Outcome and Length of Hospital Stay

Overall, 19 patients (76%) stayed in the hospital for 1 month or less while 6 (24%) stayed for more than 1 month. All patients had improved outcome after a mean length of 25 hospital days (range: 5-60 days) with no mortality. None were considered cured since only decrease in size without complete resolution of the abscess, was documented in all patients on repeat imaging.

ASSOCIATION OF VARIABLES WITH OUTCOME AND COMPLICATIONS

Since all patients had improved outcome, only the analysis of variables with the presence or absence of complications was done. Complications were common in 83% (5/6) of patients aged 10-18 years old, in half (50%) of all malnourished patients, among those without co-morbid conditions (53%) and among those who were diagnosed early within less than 2 weeks (Table 3). Eleven (92%) patients with complications were also noted to be male. Similarly, 73% (11/15) of all male patients developed complications. Fisher exact test showed significant result when gender was analyzed with the development of complications (p 0.004). Logistic regression on gender showed significant difference (p 0.008), with the odds of female patients having complications from hepatic abscess at 96% (1-0.4) less than male patients (Table 4). Meanwhile, no significant differences were established between the age group, presence of co-morbidities, nutritional status, as well as time to diagnosis, and the presence of complication (Table 3).

TABLE 3: ASSOCIATION OF DEMOGRAPHIC AND CLINICAL VARIABLES WITH DEVELOPMENT OF COMPLICATIONS FROM HEPATIC ABSCESS

DEMOGRAPHIC / CLINICAL PROFILE	WITH COMPLICATIONS n=12	WITHOUT COMPLICATIONS n=13	TOTAL N= 25	P value
Age	3 (33%)			
0-2 years old	4 (40%)	6 (67%)	9 (36%)	
3-9 years old	5 (83%)	6 (60%)	10 (40%)	**0.16**

10-18 years old		1 (17%)	6 (24%)	
Gender				
Male	11(73%)	4 (27%)	15 (60%)	**0.004**
Female	1 (10%)	9 (90%)	10 (40%)	
Co-morbid condition				
Present	2 (33%)	4 (67%)	6 (24%)	**0.64**
Absent	10 (53%)	9 (47%)	19 (76%)	
Nutritional status				
Normal	5 (50%)	5 (50%)	10 (40%)	
With malnutrition	7 (50%)	7 (50%)	14 (56%)	**1.00**
Moderate Malnutrition	4 (57%)	3 (43%)	7 (28%)	
Severe Malnutrition	3 (43%)	4 (57%)	7 (28%)	
Obese	0 (0%)	1 (100%)	1 (4%)	
Time to diagnosis				
< 2 weeks	7 (58%)	5 (42%)	12 (48%)	**0.34**
≥ 2 weeks	5 (38%)	8 (62%)	13 (52%)	

TABLE 4: LOGISTIC REGRESSION ANALYSIS OF GENDER IN ASSOCIATION WITH HEPATIC ABSCESS COMPLICATIONS

	Odds Ratio	P>|z|	[95% Conf. Interval]
Gender			
Male			
Female	.040404	**0.008**	.0038083 .4286679

Fifty eight percent of the group with complications (7/12) took 2 weeks to 1 month for symptom resolution while 83% percent (10/12) of those with complications, stayed in the hospital for less than a month. No statistical significance was noted between these two variables and having complications (p 0.32, p 0.64, respectively).

Fever with one associated symptom was a frequent finding in 58% (7/12) of complicated hepatic abscess. On further subanalysis, it was demonstrated that large abscesses size > 5 cms were common among patients having fever with 1 or 2 associated symptoms (73% and 67% respectively), and all who presented with fever alone (100%) had abscess size of < 5 cms. However, the clinical manifestations had no significant association with complications (p 0.71), and the abscess size (p 0.11).

Complications were seen in 7 patients (37%) with anemia and in 12 patients (50%) with leukocytosis (Table 5). Elevated white cell counts were found among all complicated hepatic abscesses. Similarly, no significant difference was seen between the occurrence of complications and the findings of anemia (p 0.07) and leukocytosis (p 1.00) on CBC.

Growth positivity to hepatic abscess culture and blood culture in association with complications, likewise, did not show any significant difference with p values of 1.0 and 0.60, respectively (Table 5).

TABLE 5. ASSOCIATION OF LABORATORY RESULTS WITH DEVELOPMENT OF COMPLICATIONS FROM HEPATIC ABSCESS

Laboratory Profiles	WITH COMPLICATIONS n=12	NO COMPLICATIONS n=13	TOTAL N=25	P value
Anemia				
Present	7 (37%)	12 (63%)	19 (76%)	
Absent	5 (83%)	1 (17%)	6 (24%)	0.07
Leukocytosis				
Present	12 (50%)	12 (50%)	24 (96%)	
Absent	0 (0%)	1 (8%)	1 (4%)	1.00
HEPATIC ABSCESS CS				
Positive	3 (60%)	2 (40%)	5 (20%)	
No growth	2 (50%)	2 (50%)	4 (16%)	1.00
Not done	7(58%)	9 (70%)	16 (64%)	
BLOOD CS				
Positive	3 (75%)	1 (25%)	4 (16%)	
No growth	8 (53%)	7 (47%)	15 (60%)	0.60
Not done	1 (17%)	5 (83%)	6 (24%)	

TABLE 6. ASSOCIATION OF DIAGNOSTIC RESULTS WITH COMPLICATIONS FROM HEPATIC ABSCES

CHARACTERISTICS OF HEPATIC ABSCESS ON IMAGING	WITH COMPLICATIONS n=12	NO COMPLICATIONS n=13	TOTAL N=25	P value
Abscess size				
≤ 5 cms	4 (40%)	6 (60%)	10 (40%)	0.69
>5 cms	8 (53%)	7 (47%)	15 (60%)	
Hepatic lobe involvement				
Right	11 (61%)	7 (39%)	18 (72%)	
Left	1 (33%)	2 (67%)	3 (12%)	0.09
Right and left	0 (0%)	4 (100%)	4 (16%)	
Number of abscess				
Solitary	10 (83%)	9 (31%)	19 (76%)	0.64
Multiple	2 (17%)	4 (69%)	6 (24%)	

Eight (67%) of the complicated cases had abscess size of > 5 cms, with 11 (92%) complicated cases having right hepatic lobe involvement and 10 (83%) being solitary (Table 6). Among the different imaging characteristics analyzed, none were found to have significant association with complications having p values of 0.69, 0.09 and 0.64, for the size, lobe involvement and number of abscess, respectively. In this study, half of the patients with complications (6/12) were treated with antibiotics alone and half

(6/12) were managed using surgical drainage aside from antibiotics. Four out of thirteen (31%) patients without complications were treated with both antibiotics and surgical decompression. No statistical difference was demonstrated between the development of complications and the mode of treatment applied (p 0.43).

DISCUSSION

Hepatic abscess is a frequently encountered condition in tropical and subtropical zones[13] like the Philippines. However, our data shows that its occurrence in children is quite rare. It affects the younger population especially males[14], and the earlier age trend among patients from developing countries may be due to earlier contact with infection[5]. Similarly, in this study, the mean age in years was 5.27 +/- 4.8 SD with male predominance. Although male susceptibility was described mostly for adults, male children, likewise, are affected more than females[2]. This male predominance may be explained by a study in mice where activation of natural killer T cell-producing interferon gamma, important for liver abscess control, is influenced by the inhibiting effect of testosterone[15].

Children have distinctive set of predisposing causes for hepatic abscess. Co-morbid conditions similar to the findings of one study[16] like intestinal parasitism, pulmonary tuberculosis and skin infection were observed in 24% of our cases, with malnutrition in 56% of patients. Trauma, which is also a commonly reported factor, however, was not reported in our patients.

Fever in hepatic abscess usually presents as fever of unknown origin[1,16]. Two studies described fever and abdominal pain as the most frequent symptoms in hepatic abscess[5,17], which were consistent in this study.

There were limitations in the laboratory findings from this study since only complete blood count was common to all patients. The anemia and leukocytosis seen in our patients, were also noted by Mishra, et al, regardless of etiology of hepatic abscess[13].

About 2/3 of cases of hepatic abscess in developing countries are amoebic in origin and ¾ of cases in developed countries are pyogenic[13]. The predominant organism cultured from our patients' hepatic abscesses was *Staphylococcus aureus*, which is the most common pyogenic cause in children[14], in contrast to *Escherichia coli* and *Klebsiella pneumonia* in adults[18,19]. Likewise, there was monomicrobial growth in blood culture of our patients with *Staphylococcus aureus*. An adult study in 2011 reported a polymicrobial cause for hepatic abscess[20]. In our case, 64% of patients had no definitive diagnosis from hepatic abscess culture. Sensitive markers for amoebic infection like indirect hemagglutination assay or enzyme immunoassay are not commonly used in our setting because of limited availability and high cost. Hence, the possibility of an isolated pyogenic, or a concomitant amoebic cause for hepatic abscess in our patients cannot be confirmed.

Both amoebic and pyogenic hepatic abscesses are frequently identified in the right lobe[14]. While pyogenic abscesses can be both solitary and multiple, solitary abscesses are mostly amoebic in origin[14,21]. We found a predominance of solitary and large ($\geq$ 5 cms) abscesses mostly involving the right lobe among our patients. The latter finding is due to the greater volume of the right lobe and streaming effect of portal venous blood flow[3].

Amoebic liver abscess is the most common extraintestinal site of amoebic infection but occurs only in <1% of *Entamoeba histolytica* infections. It usually presents with fever, with ~ 10-20% having past history of diarrhea or dysentery. Upper abdominal pain is usually intense and constant and its cardinal sign is tender hepatomegaly. Indirect

hemagglutinin assay is the most sensitive test (90%)[22], however, this has been replaced by the more commercially available Enzyme Immunoassay (EIA) test kits for routine serodiagnosis of amoebic infections[23]. However, in our clinical setting, it is not readily available and costly hence, empiric treatment for both pyogenic and amoebic causes becomes an option.

The standard management for both pyogenic and amoebic hepatic abscess, was observed among our patients. A two-week systemic antibiotic therapy followed by a four-week course of appropriate oral agent plus metronidazole for 10 days was the usual regimen seen in our study. There has been much debate over the role of either percutaneous or open surgical drainage. In addition to abscess size, other criteria for percutaneous drainage include: continued fever after 2-3 days of adequate medical treatment, and clinical or ultrasonographic features suggest impending perforation[24]. Insertion of a drainage catheter was more effective for abscesses larger than 5 cm[25], requiring fewer secondary procedures, and achieved higher rates of resolution[26]. Sixty percent of our patients were treated conservatively with antibiotics alone, 53% of whom had abscess size of > 5 cms. Majority of those who underwent percutaneous drainage had abscess size $\leq$ 5 cms, while those which were drained openly were > 5 cms in size. Records did not clearly state why some patients underwent surgical intervention and others did not.

All patients had improved outcome, with an average of 34 days for symptom resolution and an average of 25 hospital days. The prolonged hospital stay and symptom resolution observed were confounded by factors such as missed doses of antibiotics, delay in facilitating diagnostics, or even delay in hospital discharge for socioeconomic reasons.

Mortality rates were reported to be as high as 36%, although they have decreased in more recent publications[5,7,27]. The absence of mortality in our study probably reflects the early diagnostic and therapeutic interventions as well as the targeted and prolonged intravenous antibiotic therapy, similar to the findings of Tsai, et al [27,28]. Another reason may possibly be due to the etiology of the abscess.

Intraperitoneal rupture with peritonitis, hepatopleural or hepatobronchial fistulae and pericardial extension are the common complications noted[13]. Pleuropulmonary complications, ascites, peritonitis, septic shock, and, rarely, perforations also occur[17,29]. The most common complication encountered in this study was pleural effusion.

There are few studies done among children on factors affecting complications and outcome in hepatic abscess. Patient's age, multiplicity of abscesses and organisms, and presence of immunosuppressive conditions were some of the poor prognostic factors identified for morbidity and mortality[30]. Among the factors analyzed in this study, only male gender had significant difference in the occurrence of complications from hepatic abscess. This finding was not demonstrated in other studies and in our case, may be explained by the predominance of male subjects with hepatic abscess.

CONCLUSION & RECOMMENDATIONS

Hepatic abscess was identified in 25 pediatric cases within 19 years, commonly in younger and male group. Fever was the most common presentation and, anemia and leukocytosis were frequent laboratory findings. There were only a limited number of patients who had hepatic abscess culture, in which, *Staphyloccoccus aureus* was the most common organism isolated, however, a concomitant amoebic cause cannot be ascertained. Majority of the abscesses on imaging were solitary, > 5 cms in size involving the right lobe. All had improved outcome

with no mortality noted, but with complications that included pleural effusion, extension, peritonitis and rupture. Only male gender was found to be statistically significant as a factor for developing complications.

Prospective studies with determination of specific etiologic cause (pyogenic or amoebic) of hepatic abscess in children and the efficacy of the different treatment modalities are recommended. Evaluation of the need for CT scan for its diagnosis is likewise recommended. Long-term outcome of children who have had hepatic abscess is likewise an important aspect to look into.

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ORIGINAL ARTICLE

Effectiveness of Public Health Education by Lecture on Improving the Knowledge, Attitude, and Practices on Leptospirosis Among Adolescents in a Public School in Manila

Jenna Angela D. Rubio, MD*

*Pamantasan ng Lungsod ng Maynila

Correspondence:
Dr. Jenna Angela D. Rubio
Email: jennadrubio@gmail.com

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

ABSTRACT

Leptospirosis is endemic worldwide. Based on the 2016 Philippine Pediatric Society Disease Registry, there were 800 cases of leptospirosis from May 2006 to August 2016, making it a significant public health concern. Case fatality rate is about 8-9%, with increased prevalence of the disease among adults and adolescents.

Objective: This study was conducted to evaluate the effectiveness of public health education through a lecture on improving the knowledge, attitude, and practice scores on leptospirosis among adolescents from grades 7-10 in a public school in Manila.

Methodology: This was a cross-sectional analytical study. A pre-tested, self-administered questionnaire was given among 357 students in a public school in Intramuros, Manila. A lecture regarding leptospirosis was conducted and a post-test was given afterwards. Data was analyzed using paired t-test.

Results: A total of 357 students were included, with an 88.37% response rate. Total mean pre-test knowledge score was 88.64%, and total mean pre-test attitude score was 80.97%. For practices related to leptospirosis, the total mean pre-test score was 72.12%. Pre-test knowledge scores were compared with post-test scores. After the lecture, there was a significant increase in their knowledge on leptospirosis (p=<0.0001). There was also an improvement on post-test scores on attitude and practices regarding leptospirosis (p=<0.0001).

Conclusion: Public health education through a lecture was effective in increasing the knowledge, attitude, and practice scores on leptospirosis among adolescents. This may help in the prevention of the disease in the adolescent population.

KEYWORDS: *Leptospirosis, Adolescence, Public Health Education*

INTRODUCTION

Leptospirosis is a zoonotic disease endemic worldwide in tropical and subtropical countries, and in urban and rural settings. The mean annual global incidence of epidemic leptospirosis as reported in outbreaks, was 14 cases per 100,000 population [1] however, prevalence rates worldwide remain underreported. In the Philippines, leptospirosis peaks during the rainy months of July to October. In 2012, there were 6,439 cases recorded, with 141 fatalities.[2] There were 350 suspect cases reported nationwide from January to July 2015[3] with 33 deaths during the same time period, accounting for 9.43% of all cases. The disease mostly occurs in the 25 to 39 year age group (37.4%), followed by those 15-24 years old. Based on the 2016 Philippine Pediatric Society Disease Registry, there were 800 cases of leptospirosis from May 2006 to August 2016.

Researches regarding knowledge, attitude, and practices on leptospirosis among different populations have been done. In rural Peru the potential relationship of environmental context to human exposure to *Leptospira* showed that low level of education and living close to the river were risk factors for leptospiral seropositivity. Conversely, prevalence of anti-leptospiral antibodies decreased with education and was most likely associated with a greater degree of personal hygiene.[4]

In Thailand, Wiwanitkit in 2006 conducted a knowledge survey among villagers in an endemic area which showed that 80% of subjects had poor knowledge on leptospirosis, 11% had fair knowledge, and only 9% had good knowledge of the disease.[5] There was no significant correlation with the sex and age of subjects and their knowledge of leptospirosis. However, there was a significant correlation with the level of education and occupation and their knowledge of the disease.

In India, studies were done among workers at risk for leptospirosis - garbage collectors, drainage cleaners and septic tank cleaners. Majority had poor knowledge (87.2%) and unsatisfactory practice scores (64.5%) but had satisfactory attitude scores (64.9%).[6] Sources of information were the television (55%), newspaper (20%), and both television and newspaper (25%). A similar study in Malaysia showed that majority of town service workers had poor knowledge (87.2%) and unsatisfactory practice scores (64.5), while 64.9% had satisfactory attitude scores. [7] In India, an awareness study involving the general population through a questionnaire, showed that there is only a 27% awareness on leptospirosis. In an urban slum in Brazil, another study showed that 90.3% have heard about leptospirosis and 76.6% of them know that leptospirosis is a disease.[8] More than half of respondents know its mode of transmission. Only half recognized that the disease requires prevention and control strategies, and 35% observed protective measures such as wearing gloves and boots while cleaning the sewers.

In Western Jamaica, the association between potential risk factors and clinical leptospirosis was studied and showed that both occupational and environmental exposures had an effect on the occurrence of leptospirosis.[9]

In the local setting, several studies were done on leptospirosis-related knowledge, attitude, and practices. Quina et al.[10] focused on health workers and barangay officials and selected residents in Samar. It showed that majority of respondents were knowledgeable on leptospirosis. They practiced prevention and control strategies such as maintaining cleanliness of surroundings and proper hygiene. The health workers and barangay

officials "frequently" practiced them while barangay residents "always" practiced them.

A study in Laguna focused on agricultural and non-agricultural workers. It showed that the total mean knowledge score for all respondents was 68.50%. However, total mean knowledge scores between the 2 groups were not statistically significant. The total mean attitude score of all respondents (80.80%), was higher than their total mean knowledge (68.50%) and practice scores (61.28%). [11]

A study on the association between leptospirosis-related knowledge and practices of pedicab drivers in Manila showed that 49% have correct knowledge on transmission and prevention of leptospirosis, while 21% had satisfactory preventive and health-seeking practices. This also showed that low level of education and poor knowledge had an effect on practices.[12]

Older age and income level were significantly associated with preventive practices among agricultural workers.[11] Still another study showed that respondents needed to have proper information regarding the disease to understand and observe preventive control strategies against leptospirosis. [9]

Although most KAP studies on leptospirosis were done in adults, one study among adolescents in Sri Lanka showed that there was a 'good' level of knowledge on leptospirosis in 52% of the study population.[13] Parents' involvement in paddy cultivation was measured and was found to be significantly associated with the level of knowledge of participants on leptospirosis. None of personal prevention practices were significantly associated with level of knowledge, suggesting that knowledge alone is not sufficient to improve on practices.[13]

Most studies concluded that education and promotional activities are needed to increase knowledge on the disease. An intervention, such as a lecture however was not done hence, this study aimed to determine the effectiveness of public health education through a lecture on improving the knowledge, attitude, and practice scores on leptospirosis among adolescents from grades 7 to 10 in a public school in Manila.

METHODOLOGY

Ethics Approval

Written approval was obtained from the Department of Education and school Principal of Manila High School in Intramuros, Manila prior to the conduct of the study. Approval was also obtained from the Ethics Review Committee of the Department of Pediatrics and the Hospital Research Committee.

A written informed consent and assent were obtained from the parents/ guardian and students respectively. The parents were informed of their right to withdraw their child's participation any time during the study. Measures were observed to maintain confidentiality and all information were used for research purposes only.

STUDY DESIGN

This was a cross-sectional analytical study.

STUDY POPULATON

A school-based study was done in a public school in Intramuros, Manila. Students who belong to Grades 7 to 10, with ages 12 to 18 years old, and enrolled at Manila High School for the year 2016-2017 were included in this study. Excluded were those who did not give their consent as well as those who participated in the pre-test.

The sample size was computed using Lwanga and Lemeshow formula. The level of confidence was set at 95% with the normal z-deviate of 1.96. The acceptable

maximum error was 5%.

$$n = \frac{z^2 pq}{d}$$

where n = desired sample size
z = normal z-deviate
p = population proportion
q= 1-p
d = confidence interval

$$n = \frac{1.96^2 x\ 0.5\ x\ 0.5}{.05}$$

$$n = 384$$

The computed sample size was adjusted for a 5% non-response rate.

$$N = \frac{n}{response\ rate}$$

$$N = \frac{384}{1 - 0.05}$$

$$N = 404$$

Data Collection

The questionnaire was pre-tested among a group of 40 students who shared similar characteristics with the study population. The items in the questionnaire were based on validated questions from a previous study by Arbiol et al (2016) with modifications. Content validation of the questionnaire was made by experts on the topic (nephrology and infectious disease consultants).

The questionnaire comprised of 4 sections. The 1st section determined the demographic profile of the students as to age, sex, grade level, family income, means of transportation, and source of information on the disease.

The 2nd section assessed the knowledge of the subjects on leptospirosis: causative agent, mode of transmission, signs and symptoms, complications, and methods of prevention and control. This section consisted of questions answerable with yes/no/I don't know. A score of 1 was given for a "Yes", and a score of 0 for "No" or "I don't know". The total knowledge score for each student ranged from 0 to 11.

The 3rd section evaluated the attitude of the students towards leptospirosis. The students were asked about their level of agreement on statements about leptospirosis, including the seriousness of the disease, its preventable and treatable nature, and the importance of protective measures such as rat control and early health-seeking behaviors. It consisted of a four-level Likert scale question format (1-strongly disagree, 2-disagree, 3-agree, 4-strongly agree), with an acceptable level of reliability. The total attitude score for each student ranged from 5 to 20.

The 4th section assessed practices related to leptospirosis, such as use of protective wear, personal hygiene, rat control measures and health seeking behaviors. It consisted of a four-level scale question format (1-never, 2-sometimes, 3-often, 4-always), with an acceptable level of reliability. The total practice score for each student ranged from 6 to 24.

The master lists of sections from Grades 7-10 were requested and the sections were randomly selected by lottery. The same method was done to select the students who were included in the study. Those who were selected were provided with a self-administered pre-test questionnaire after the study objective was explained to the students. The subjects were given 10-15 minutes to answer the questionnaire. A lecture was given afterwards and a visual aid in the form of handouts were provided during the lecture. The content of the lecture was on leptospirosis, its causative agent, transmission, signs and symptoms, management, and prevention. A self-administered post-test questionnaire was given to the students 5 minutes after the lecture.

Data were encoded using Epi Info 7. Paired t-test was used to determine if there is a significant difference on the level

of knowledge, attitude and practice scores on leptospirosis before and after the lecture.

RESULTS

A total of 357 students were included in this study, with an 88.37% response rate. The rest of the students who were included but were not present during data collection were considered dropouts. Table 1 shows the demographic profile of participants. Majority were female, (n=189 students, 52.94%) with a male to female ratio of 0.89. The mean age of participants is 14 years old. Grade 8 had the highest number of students (n=92, 25.77%). Majority belonged to families with an income of less than Php 10,000/month. The most common mode of transportation for students is by public transport through jeepney or tricycle or "pedicab".

Table 1. Demographic Profile of Adolescent Students in a Public School in Manila

Demographic Profile	Frequency (Percentage) (n= 357)
Sex	
Male	168 (47.06%)
Female	189 (52.94%)
Age (in years)	
12	56 (15.69%)
13	53 (14.85%)
14	77 (21.57%)
15	91 (25.49%)
16	54 (15.13%)
17	17 (4.76%)
18	9 (2.52%)
Grade	
7	89 (24.93%)
8	92 (25.77%)
9	87 (24.37%)
10	89 (24.93%)
Income	
< Php 10,000	182 (50.98%)
Php 10, 000 – 19,999	127 (35.57%)
Php 20,000 – 29,999	36 (10.08%)
> Php 30,000	12 (3.36%)
Mode of Transportation	
Walking to and from school	94 (26.33%)
Riding a jeep/tricycle/pedicab	261 (73.11%)

Table 2 shows where different sources of information on leptospirosis are derived. The television is the most common source of information (65.27%), followed by public health services (14.57%) and the school (6.44%). About 3.08% of the study population said that they have not heard of leptospirosis.

Table 2. Source of Information on Leptospirosis among Adolescent Students in a Public School in Manila

	Frequency (Percentage) (n= 357)
Source of Information	
TV	233 (65.27%)
School	23 (6.44%)
Family	18 (5.04%)
Friends/Neighbor	2 (0.56%)
Public Health services	52 (14.57%)
Internet	18 (5.04%)
Newspaper	0 (0%)
I haven't heard about leptospirosis	11 (3.08%)

Table 3 shows the knowledge, attitude, and practice scores of study participants. The total mean pre-test knowledge score for all participants was 88.64%. Questions pertaining to disease prevention had the highest mean score of 93.91%, followed by mode of transmission, 93.46%. Questions about signs and symptoms had the lowest mean score of 79.50%.

For attitude on leptospirosis, the total mean pre-test attitude score for all participants was 80.97%, while practices related to leptospirosis had a total mean pre-test score of 72.12%. With regards to item-specific practices, protective gear and safety measures (such as wearing of boots when exposed to flood, immediate cleansing after wading, and maintaining clean surroundings) had the highest mean score of 76.03%, followed by rat control measures with a score of 69.75%. Total mean score for health-seeking behavior was lowest at 67.09%.

Table 3. Knowledge, Attitude, and Practice Scores of Adolescent Students in a Public School in Manila

	Pre-Test	Post-Test		
	Mean ± S.D.	Mean ± S.D.	Difference	p-value
Total Knowledge Score	88.64 ± 1.94	98.68 ± 3.99	10.04	<0.0001
Mode of Transmission	93.46 ± 18.21	99.16 ± 6.31	5.70	<0.0001
Signs and Symptoms	79.48 ± 23.87	98.04 ± 7.23	18.56	<0.0001
Disease Prevention	93.91 ± 14.50	98.81 ± 5.95	4.90	<0.0001
Total Attitude Score	80.97 ± 13.01	88.94 ± 11.49	7.97	<0.0001
Total Practice Score	72.12 ± 11.86	76.45 ± 12.57	4.33	<0.0001
Protective gears and safety measures	76.03 ± 13.31	78.59 ± 13.61	2.56	<0.0001
Rat control measures	69.75 ± 19.24	72.93 ± 19.64	3.18	<0.0001
Health-seeking behavior	67.09 ± 23.15	70.87 ± 23.60	3.78	<0.0001

Pre-test knowledge scores were compared with post-test scores (Table 3). After an informative lecture was conducted, there was a significant increase in their knowledge on leptospirosis ($p<0.0001$) as to its mode of transmission, signs and symptoms and prevention. There was also an improvement on post-test scores on attitude towards leptospirosis ($p<0.0001$).

Comparing pre-test and post-test practice scores after the lecture, post-test scores showed that more adolescents will use protective gear and safety measures, perform rat control measures and seek timely medical consult ($p<0.0001$).

DISCUSSION

This study determined knowledge, attitude, and practices regarding leptospirosis among adolescents in a public school in Manila. It was conducted among adolescents since the disease is common in this age group.

Most of the participants are knowledgeable on leptospirosis. This finding was similar to a study done among adolescents in Sri Lanka and workers in Samar and Laguna. This may be explained by the fact that the disease is common in slum areas such as in Manila, with frequent outbreaks of leptospirosis in the country. Total mean knowledge score (88.64%) was higher than the total mean attitude (80.97%) and practice scores (72.12%). However, knowledge on signs and symptoms had the lowest mean score of 79.50%. This shows that knowledge on signs and symptoms need to be emphasized in this age group. However, after an informative lecture, there was a significant increase in their knowledge. Based on the study by Keenan in 2010, knowledge of the disease and its causes allows for protection from the disease. Proper education and awareness improves their knowledge on leptospirosis, which may help protect them from the disease.

The students were asked regarding their outlook on leptospirosis. A positive attitude was measured by concurring with statements about the disease. The total mean pre-test attitude score of students towards leptospirosis was 80.97%, which showed that most of them believe that leptospirosis is serious, treatable and preventable. The scores significantly improved after the lecture ($p<0.0001$). In the study by Samarakoon et. al., knowledge alone is not sufficient to improve personal preventive practices. A positive attitude should be complemented with the correct knowledge to enhance the ability of individuals to integrate preventive measures into practice. [11,13]

Practices of students related to leptospirosis had a total mean score of 72.12%, which is slightly higher compared with the study of Arbiol et. al. The practices included in this study were swimming or playing in floodwater, wearing boots when wading in floodwater, and immediate washing of feet with soap after wading in flood. These practices had the highest mean score among the practices measured. Since this study was conducted in an area where flooding is frequent, people living in the area are familiar with protective measures. Rat control measures include cleaning the surroundings and storing food in sealed containers. After the

lecture, the post-test total mean scores were found to be statistically significant from the pre-test total mean score (p=<0.0001). Young age and low-income groups were less likely to engage in leptospirosis preventive practices, hence campaigns and strategies to improve these behaviors would be valuable in these population.

Total mean score for health-seeking behaviors was 67.09%, which was the lowest among the practices measured. In the study by Lim et al.[11], it was noted that the interaction of poor knowledge and low educational attainment could increase the odds of having unsatisfactory preventive and health-seeking practices. In this study, after the lecture was conducted, there was a significant increase in post-test scores for health seeking behavior. This means that increasing the knowledge of the students about the disease may also improve on their health-seeking behavior.

The most common source of information for this population was television, which is the same in other studies. The positive association between broadcast media and leptospirosis prevention practices is consistent with previous findings, indicating that mass media can produce positive changes or prevent negative changes in health-related behaviors [11,]. Information dissemination and awareness must be heightened through broadcast media. Practical ways to prevent leptospirosis through educational campaign by fliers, posters, and awareness campaigns in schools and through social networking may also be done.

CONCLUSION

This study determined the knowledge, attitude and practices on leptospirosis among adolescents in a public school in Manila. The effect of public health education through a lecture about the disease was measured. The results showed that there is a significant increase in knowledge, attitude, and practice scores of students after the lecture was provided.

An important finding in this study was that increasing awareness regarding leptospirosis may help in the prevention of the disease in the adolescent population.

The young and low-income groups were less likely to engage in leptospirosis prevention practices, hence campaigns and strategies to improve on such behaviors for this age group would be valuable in reducing the risk and potential economic burden of leptospirosis.

RECOMMENDATIONS

The out-of-school youth population who may have a higher probability of being exposed to the disease can be studied. Comparison of knowledge, attitude, and practices of students between private and public schools may also be done. Area of residence, physical set-up of households, and means of livelihood can be looked into in future studies, and other modes of intervention may be utilized apart from lectures.

Since the study showed positive results, it may be used by policy makers, health educators, and physicians to plan campaigns on leptospirosis, A follow-up study on the study participants may also be done to check whether the students truly understood the lecture and review whether or not they have applied what they learned.

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Panes A, Villar CM & Madrid MA. Microbiologic Profile and Predictors of Severe Outcome of Pediatric Cancer with Febrile Neutropenia Admitted at a Tertiary Medical Center

ORIGINAL ARTICLE

MICROBIOLOGIC PROFILE AND PREDICTORS OF SEVERE OUTCOME OF PEDIATRIC CANCER WITH FEBRILE NEUTROPENIA ADMITTED AT A TERTIARY MEDICAL CENTER

Andy T. Panes, MD*
Cherry May Villar, MD*
Mary Antonette C. Madrid, MD*

*Philippine Children's Medical Center

Correspondence:
Dr. Andy T. Panes
Email: andypanes01@yahoo.com

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

ABSTRACT

Background: The treatment of pediatric cancer has advanced dramatically. With the discovery of newer, more potent chemotherapeutic agents, patients are confronted with severe and prolonged degrees of neutropenia, which has inherent consequences.

Objective: The study aimed to determine common microbial isolates and predictors of severe outcome of pediatric cancer patients with febrile neutropenia aged 0-18 years old admitted at a tertiary hospital.

Methods: This was a cross-sectional study on pediatric cancer patients with febrile neutropenia admitted at the Philippine Children's Medical Center from March 1, 2017 to September 30, 2017. The clinical presentations of subjects were noted. Patients were categorized as to the presence or absence of severe outcomes. Common microbial isolates were noted. Predictors of severe outcome were identified using stepwise logistic regression analysis.

Results: Out of 105 enrolled patients, 32 developed severe outcomes. The most common isolates were *Klebsiella pneumoniae* followed by *Escherichia coli* and Candida species. Univariate analysis showed that acute myelogenous leukemia (p-value: 0.0195), treatment relapse (p-value: 0.0131), ANC on admission </= 100 cells/mm3 (p-value: 0.0001), fever of >7 days during admission (p-value: 0.0001), non-response to empiric antibiotics (p-value:0.0001), microbiologically-defined infection (MDI, p-value: 0.0001), fever without a focus (p-value:0.001), bloodstream infection (p-value: 0.0192), unknown focus of infection (p-value: 0.0058), and a positive culture (p-value: 0.0001) were related to a severe outcome. None of these predictive variables, however, were statistically significant on multivariate logistic regression analysis.

Conclusion: *K. pneumoniae*, *E. coli* and Candida were the predominant organisms identified in febrile neutropenic cancer patients in our institution. Although AML, treatment relapse, profound neutropenia, fever of >7 days during admission, non-response to empiric antibiotics, MDI, fever without a focus, bloodstream infection, unknown focus of infection and a positive culture were related to a severe outcome, multivariate regression analysis did not show these to be significant.

KEYWORDS: *Microbiologic profile, Fever, Neutropenia, Predictors*

INTRODUCTION

Febrile neutropenia refers to the occurrence of fever in a neutropenic patient undergoing cytotoxic treatment, commonly with uncontrolled neoplasm of the bone marrow [1]. Infection occurs as a consequence of immunosuppression due to the underlying disease, or from the use of cytotoxic treatment, and possibly in association with invasive procedures [2].

Clinicians handling pediatric patients with cancer are often faced with the challenge of managing episodes of febrile neutropenia. While aggressive chemotherapy improves survival of children with hematologic disorders, it carries the risk of infection, which is a major cause of morbidity and mortality in this patient population [3,4]. Epidemiologic studies demonstrate a high incidence of sepsis in pediatric patients receiving chemotherapy, in approximately 12.8% of children aged 1-9 years and 17.4% of children aged 10-19 years. This underscores febrile neutropenia as a significant complication in the treatment of childhood cancer [4].

At the Cancer and Hematology Center of the Philippine Children's Medical Center (PCMC), there were 300 febrile neutropenia cases out of 2,500 admissions in 2016. This accounted for 12% of all cases seen during this period. There were three local studies which looked into the microbiologic data of febrile neutropenia patients admitted at PCMC [5,6,7]. However, these were retrospective researches. This is the first prospective study on the microbiologic profile and predictors of severe outcome of febrile neutropenia patients in our institution. Information on identified pathogens will aid in the selection of appropriate antimicrobials for empiric therapy and promote judicious use of these agents. Insights gained on factors shown to be associated with unfavorable outcomes can influence improvements in the provision of care for this population and contribute in decreasing morbidity, mortality, and cost-related hospitalization.

MATERIALS AND METHODS

We conducted a cross-sectional study to determine microbial isolates and predictors of severe outcome of pediatric cancer patients aged 0 to 18 years with febrile neutropenia, admitted at the Philippine Children's Medical Center from March 1, 2017 to September 30, 2017.

Approval from the Institutional Review Board (IRB) and Research Ethics Committee of the Philippine Children's Medical Center were obtained prior to the conduct of the study. Informed consent and assent were sought prior to subject enrollment. Potential conflicts of interest were disclosed and patient's identities were kept confidential at all times.

The minimum sample size of 105 was calculated using power analysis by G*Power software as indicated by the returned values of the A Priori analysis. A logistic regression of a binary response variable (Y) on a binary independent variable (X) with sample size of 105 observations achieves 95% power at 0.05 level of significance.

All cancer patients 0-18 years old, undergoing chemotherapy/combination therapy and admitted due to fever and neutropenia were included in the study. Excluded are patients where chemotherapy has not started, newly-diagnosed malignancies admitted for the first time, those with existing severe infection prior to the onset of neutropenia, those with healthcare associated infections on admission, and patients on palliative care.

Patients who withdrew from the study and those who were initially enrolled but were later discharged against medical advice were considered dropouts.

Recruitment was done by the investigators upon admission at the Emergency Department. As soon as informed consent was obtained, history taking and a thorough physical examination were performed. The investigators had no direct involvement in the evaluation and management of cases. Daily observation of subjects was done

during the entire course of hospital stay until discharge. Data pertinent to the study were recorded using a case report form.

Patients were classified as belonging to either the "complicated group" if they developed a severe outcome or the "non-complicated group" if without severe outcome. Severe outcome was defined as having any of the following: hypotension (BP below the 5th percentile or below two standard deviations (SDs) of the mean for age and gender, respiratory failure (arterial oxygen pressure < 60 mmHg on room air or need for mechanical ventilation), congestive heart failure, uncontrolled arrhythmia, intensive care unit admission, and death.

Numerical variables were expressed as means or standard deviation. Clinical and microbiologic data were expressed as frequencies and percentages. Odds ratios and their 95% confidence intervals were computed and a p-value of <0.05 was considered significant. Stepwise logistic regression with backward selection strategy was employed on specific variables. The significance of the main effects of different independent variables on the outcome was determined by Multivariate analysis to establish strength of each independent variable and outcome variable. SPSS (Statistical Package for the Social Sciences) software was utilized to analyze the data.

RESULTS

A total of 105 cancer patients with febrile neutropenia were included, with 73 patients classified under the non-complicated group (70%) and 32 patients under the complicated group (30%). Table 1 shows the demographic and clinical profile of patients. More than half of patients in each group were males. The mean age of subjects was 6.9 years. The most common underlying disease in both groups was acute lymphocytic leukemia, with 56% of cases in the complicated group and 60.3% in the non-complicated group. More than half of patients in both groups were on induction chemotherapy when they developed febrile neutropenia. Profound neutropenia (defined as an absolute neutrophil count of <100 cells/mm^3) was seen in a higher percentage of patients in the complicated group (73%) than in the non-complicated group (58%). Ninety-seven percent of patients in the complicated group and all patients in the non-complicated group had fever of less than 7 days duration before admission but during hospitalization, most of the patients in the complicated group had prolonged fever lasting >7 days (78.1%) but none of those in the non-complicated group developed prolonged fever. Piperacillin-Tazobactam was the most common empiric antibiotic used for patients in both groups. Most of the patients in the complicated group did not respond to the initial empiric antibiotic (68.8%) while all but one patient in the non-complicated group responded to treatment. Most of the patients in the complicated group had Microbiologically-Defined Infection (MDI) while most patients in the non-complicated group had fever without a focus (60.3%), or Clinically-defined Infection (CDI, 35.6%). Bloodstream infection was the most common infection seen in more than half of patients in the complicated group. Unknown focus of infection (45.2%), followed by respiratory infection (23.3%) characterize most of the patients in the non-complicated group. Organisms were isolated from most of the patients in the complicated group while a majority of patients in the non-complicated group had negative culture results. All of the patients in the non-complicated group were discharged improved while only 68.8% of patients in the complicated group improved and 31.2% died. The overall mortality rate was 9.5%.

Table 1. Demographic and Clinical Profile of Pediatric Cancer Patients with Febrile Neutropenia Stratified to Non-Complicated or Complicated Group

	Outcome Frequency (%)			
Clinical Parameters		**Non-complicated Group n= 73 (70)**	**Complicated Group n= 32 (30)**	**Total n= (105)**
Age				
	Mean (SD)	6.8 (4.7)	7.3 (5.7)	6.9 (5.0)
	Median	5	5	5
	Range	1-18	2-18	1-18
Sex				
	Male	51 (69.9)	22 (68.8)	73 (69.5)
	Female	22 (30.1)	10 (31.3)	32 (30.5)
Primary Underlying Disease				
	Leukemia			
	Acute Lymphocytic Leukemia	44 (60.3)	18 (56)	62 (59.0)
	Acute Myelogenous Leukemia	7 (9.6)	9 (28.1)	16 (15.2)
	Chronic Myelogenous Leukemia	2 (2.7)	0	2 (1.9)
	Lymphoma	3 (4.1)	0	3 (2.9)
	Solid-organ Tumors	17 (23.3)	5 (15.6)	22 (21)
Type of treatment				
	Chemotherapy	72 (98.6)	32 (100)	104 (99)
	Combination	1 (1.4)	0	1 (1.0)
Status of treatment				
	On treatment			
	Induction	39 (53.4)	19 (59.4)	58 (55.2)
	Intensification	0	3 (9.4)	3 (2.9)
	Consolidation	12 (16.4)	2 (6.3)	14 (13.3)
	Maintenance	14 (19.2)	2 (6.3)	16 (15.2)
	Re-induction	4 (5.5)	0	4 (3.8)
	Remission	0	0	0
	Relapse	3 (4.1)	6 (18.8)	9 (8.6)
ANC on admission				
	</= 500 cells/mm3	31 (42.5)	9 (28.1)	40 (38.1)
	</= 100 cells/mm3	42 (57.5)	23 (71.9)	65 (61.9)
Duration of fever prior to admission				
	</= 7 days	73 (100)	31 (96.9)	104 (99.0)
	> 7 days	0	1 (3.1)	1 (1.0)
Duration of fever during admission				
	</= 7 days	73 (100)	7 (21.9)	80 (76.2)
	>7days	0	25 (78.1)	25 (23.8)
Empiric Antibiotic Used				

	Ceftazidime +/ - aminoglycosides	14 (19.2)	2 (6.3)	16 (15.2)
	Cefepime	4 (5.5)	2 (6.3)	6 (5.7)
	Piperacillin-tazobactam	55 (75.3)	25 (78.1)	80 (76.2)
	Meropenem	0 (0)	3 (9.4)	3 (2.9)
Response to antibiotic therapy				
	Responders	72 (98.6)	10 (31.3)	82 (78.1)
	Non-Responders	1 (1.4)	22 (68.8)	23 (21.9)
Infection Type				
	Microbiologically-Defined Infection (MDI)	3 (4.1)	22 (68.8)	25 (23.8)
	Clinically-Defined Infection (CDI)	26 (35.6)	8 (25.0)	34 (32.4)
	Fever of Without a Focus	44 (60.3)	2 (6.3)	46 (43.8)
Site of infection				
	Oral Cavity	12 (16.4)	3 (9.4)	15 (14.3)
	Respiratory tract	17 (23.3)	4 (12.5)	21 (20.0)
	GI/Intra-abdominal Tract	7 (9.6)	3 (9.4)	10 (9.5)
	Genito-urinary tract	1 (1.4%)	2 (6.3)	3 (2.9)
	Skin and Soft Tissue	2 (2.7)	0	2 (1.9)
	Bloodstream	0	17 (53.1)	17(16.2)
	Unknown	33 (45.2)	2 (6.3)	35 (33.3)
	Others	1 (1.4)	1 (3.1)	2 (1.9)
Isolated Organisms				
	Without	69 (94.5)	10 (31.3)	79 (75.2)
	With	4 (5.5)	22 (68.8)	26 (24.8)
Primary Outcome				
	Discharged/ Improved	73 (100)	22 (68.8)	95 (90.5)
	Expired	0	10 (31.3)	10 (9.5)

A total of 30 pathogens were isolated from 26 patients. Table 2 summarizes the isolates in both groups. More than half of the organisms were isolated from the blood (n=20, 66.7%). Four isolates were from 4 patients in the non-complicated group (5.5%) and 26 isolates were from 22 patients in the complicated group (68.8%). Most patients with positive isolates were on induction chemotherapy (54%), while some were in relapse (19%). Four patients had more than one organism which grew from different sites. Gram negative Multi-drug resistant organisms (MDROs) *Klebsiella pneumoniae, Escherichia coli, Enterobacter cloacae,* and *Pseudomonas aeruginosa*, were the predominant isolates (n=12, 40%), followed by gram negative non-Multidrug-resistant organisms (non-MDROs; n=12, 40.0%). Three *Klebsiella pneumoniae* were found to be Extensively Drug-Resistant Organisms (XDROs) and were sensitive only to amikacin and/or colistin. *Klebsiella pneumoniae* was the most common isolated organism (n=10, 33%), followed by *Escherichia coli* (n=9, 30%) and Candida species (n=5, 17%). Eight of 10 *K. pneumoniae* isolates and 5 of 9 *E. coli* isolates were Extended Spectrum Beta-lactamase-producing (ESBL-producing) bacteria. A summary of the distribution of isolates is summarized in Table 3.

Table 2. Microbiologic Profile of Patients with Febrile Neutropenia

		Non-complicated Group n: 4 (%)	**Complicated Group** n: 26 (%)	**Total** n: 30 (%)
Isolated Organisms				
	Gram positive bacteria, *Non-MDRO	0	0	0
	Gram positive bacteria, **MDRO	1 (25.0)	2 (7.7)	3 (10.0)
	Gram negative bacteria, Non-MDRO	2 (50.0)	5 (19.3)	7 (23.3)
	Gram negative bacteria, MDRO	1 (25.0)	11(42.3)	12 (40.0)
	Gram negative bacteria, ***X-DRO	0	3 (11.5)	3 (10.0)
	Fungus	0	5 (19.2)	5 (16.7)

(Four patients had 2 organisms isolated from different sites)
**Non-MDRO- Non multidrug-resistant organism*
***Multidrug-resistant organism*
****Extensively drug-resistant organism*

Table 3. Distribution of Microbial Isolates Based on Specimen Site

Specimen Site	ISOLATED ORGANISMS											
	K. pneumonia		*E. coli*		*P. aeroginosa*		*E. cloacae*		COPS**	CONS***	Candida	TOTAL
	(+)ESBL*	(-)ESBL	(+)ESBL	(-)ESBL	(+)ESBL	(-)ESBL	(+)ESBL	(+)ESBL	(+)MRSA			n:30(%)
Blood	7	1	2	2	-	1	1	-	1	1	4	20(66.7)
Urine	1	1	-	1	1	-	-	-	-	-	1	5 (16.6)
Stool	-	-	2	1	-	-	-	-	-	-	-	3 (10.0)
Wound	-	-	1	-	-	-	-	-	1	-	-	2 (6.7)
TOTAL n:30	10		9		2		1		2	1	5	
Percentage (%)	30		30		7		3		7	3	17	

**ESBL- Extended Spectrum Beta Lactamase*
**COPS- Coagulase Positive S. aureus*
****CONS- Coagulase Negative Staphylococcus MRSA- Methicillin-Resistant S. aureus*

Tables 4, 5, and 6 show the resistance patterns of isolated organisms. *Klebsiella pneumoniae* showed in vitro resistance to major antimicrobial drugs used in the treatment of febrile neutropenia as follows: Ceftazidime (80% resistance), Cefepime (80%), Piperacillin-tazobactam (70%), Meropenem (40%), Gentamicin (50%), and Amikacin (10%). *Escherichia coli* in vitro resistance to Ceftazidime, Cefepime, Piperacillin-tazobactam, Meropenem, Gentamicin and Amikacin were 89%, 78%, 78%, 22%, 44%, and 33% respectively. *Pseudomonas aeruginosa* showed no resistance to major antimicrobial drugs used in the treatment of febrile neutropenia. *Enterobacter cloacae* had 100% in vitro resistance to Ceftazidime, Piperacillin-tazobactam and Gentamicin, but was susceptible to Cefepime, Amikacin, and Meropenem. All of the isolated gram-negative organisms showed no resistance to Colistin. *Staphylococcus aureus* and coagulase negative

Staphylococcus showed 100% in vitro resistance to Oxacillin. The Candida isolates showed no in vitro resistance to major antifungal drugs such as Amphotericin, Flucytosine, Fluconazole and Voriconazole.

Table 4. Resistance Rates of Gram-Negative Organisms in Patients with Febrile Neutropenia

	K. pneumonia **n: 10**	***E. coli*** **n: 9**	***P. aeruginosa*** **n: 2**	***E. cloacae*** **n: 1**
Ceftriaxone	8 (80)	6 (67)	2 (100)	1 (100)
Ceftazidime	8 (80)	8 (89)	0	1 (100)
Cefepime	8 (80)	7 (78)	0	0
Piptazobactam	7 (70)	7 (78)	0	1 (100)
Gentamycin	5 (50)	4 (44)	0	1 (100)
Amikacin	1 (10)	3 (33)	0	0
Ciprofloxacin	6 (60)	7 (78)	0	1 (100)
Levofloxacin	1 (10)	7 (78)	0	1 (100)
Imipenem	5 (50)	2 (22)	0	0
Meropenem	4 (40)	2 (22)	0	0
Colistin	0	0	0	0

[n= Total number of isolates (% Resistance)]

Table 5. Resistance Rates of Gram-Positive Organisms in Patients with Febrile Neutropenia

	Coagulase Positive *S. aureus* *MRSA **n: 2**	**Coagulase Negative Staphylococcus** **n: 1**
Oxacillin	2 (100)	1 (100)
Clindamycin	0	0
Vancomycin	0	0
Linezolid	0	0

[n= Total number of isolates (% Resistance)]
**MRSA- Methicillin-Resistant S. aureus*

Table 6. Resistance Rates of Candida Species in Patients with Febrile Neutropenia

	Candida Species **n: 5**
Amphotericin	0
Flucytosine	0
Fluconazole	0
Voriconazole	0

[n= Total number of isolates (% Resistance)]

Table 7 shows the univariate analysis of predictive factors related to severe outcome in patients with febrile neutropenia. Variables that were determined to be related to severe outcome include: Acute myelogenous leukemia (p-value: 0.0195), treatment relapse (p-value: 0.0131), ANC on admission of </= 100 cells/mm3 (p-value: 0.0001), fever of >7 days during admission (p-value: 0.0001), microbiologically-defined infection (p-value: .0001), non-response to empiric antibiotic therapy (p-value:0.0001), fever without a focus (p-value:0.001), bloodstream infection (p-value: 0.0192), unknown focus of infection (p-value: 0.0058), and a positive culture or presence of isolated organisms (p-value: 0.0001).

Table 7. Predictive Factors Related to Severe Outcome Based on Univariate Analysis

Variables		**O.R. (95% CI)**	***p*- value (<.05)**
Age		2.26 (0.04-11.48)	0.6849
Sex			
	Male		
	Female	0.95 (0.38-2.33)	0.9092
Primary Underlying Disease			
	Leukemia		
	Acute Lymphocytic Leukemia	0.80 (0.34-1.86)	0.6038
	Acute Myelogenous Leukemia	3.69 (1.23-11.03)	<0.0195
	Chronic Myelogenous Leukemia	0.44 (0.02-9.42)	0.5995
	Lymphoma	0.31 (0.02-6.18)	0.4428
	Solid-organ Tumors	0.61 (0.20-1.83)	0.3775
Type of treatment			
	Chemotherapy	1.34 (0.05-33.91)	0.8572
	Combination		
Status of treatment			
	On treatment		
	Induction	1.27 (0.55-2.96)	0.5728
	Intensification	17.44 (0.87-348.17)	0.0613
	Consolidation	0.34 (0.07-1.61)	0.1738
	Maintenance	0.28 (0.06-1.32)	0.1074
	Re-induction	0.31 (0.02-6.18)	0.4428
	Remission	2.26 (0.04-114.48)	0.6849
	Relapse	8.19 (1.55-43.18)	<0.0131
ANC on admission			
	</= 500 cells/mm3		
	</= 100 cells/mm3	1.89 (0.77-4.64)	<0.0001
Duration of fever prior to admission			
	</= 7 days		
	> 7 days	0.14 (0.01-3.60)	0.2374
Duration of fever during admission			
	</= 7 days		
	>7days	0.0 (0.00-0.04)	<0.0001
Response to Antibiotic Therapy			
	Responders		
	Non-responders	0.01 (0.00—0.05)	<0.0001
Infection Type			

	Microbiologically-Defined Infection (MDI)	51.33 (12.96-203.29)	<0.0001
	Clinically-Defined Infection	0.60 (0.24-1.53)	0.2871
	Fever of Without a Focus	0.05 (0.01-0.21)	<0.0001
Site of infection			
	Oral Cavity	0.53 (0.14-1.53)	0.3472
	Respiratory tract	0.47 (0.14-1.53)	0.2105
	GI/Intra-abdominal Tract	0.98 (0.24-4.04)	0.9726
	Genito-urinary tract	4.80 (0.42-54.96)	0.2073
	Skin and Soft Tissue	0.44 (0.02-9.42)	0.5995
	Bloodstream	62.49 (3.5-1116.8)	<0.0192
	Unknown	0.02 (0.00-0.32)	<0.0058
	Others	2.32 (0.14-38.33)	0.5558
Isolated Organisms			
	Without		
	With	37.95 (10.82-133.11)	<0.0001

Table 8 shows the Multivariate Logistic Regression Analysis to identify predictors of severe outcome. The model was statistically significant $\chi 2$ (32) = 129.117, p <.000. This explained 70.8% (Cox & Snell R2) of the variance in severe outcome in patients with febrile neutropenia and correctly classified 100% of cases. However, none of the variables that were determined to be related to severe outcome on univariate analysis reached statistical significance on multivariate regression analysis.

Table 8. Multivariate Logistic Regression Analysis Predicting Likelihood of Developing Severe Outcome

		Odds Ratio	**95% CI for Odds ratio**		***p*-value (<.0000)**
			Lower	**Upper**	
Primary Underlying Disease					
	Acute Myelogenous Leukemia	0.000	0.000	-	0.999
Status of treatment					
	Relapse	1.497	0.000	-	1.000
ANC on admission					
	< 100 cells/mm^2	105926.326	0.000	-	0.999
Duration of fever during admissiion					
	> 7 days	3.179E+16	0.000	-	0.998
Empiric Antibiotic Therapy					
	Non-responders	8.811E+14	0.000	-	0.998

Infection type					
	Microbiologically-identified Infection				
	Fever without a focus	0.000	0.000	-	1.000
Site of infection					
	Bloodstream				
	Unknown	0.000	0.000	-	0.999
Isolated organisms					
	With	0.000	0.000	-	1.000

DISCUSSION

Life-threatening infection is a common consequence of febrile neutropenia which develops among pediatric cancer patients receiving chemotherapy. Our study showed that 30% of our subjects developed severe outcome that resulted to mortality in 9% of those in the complicated group. Mortality rate in patients with febrile neutropenia documented in other studies ranged from 5 to 21%. [8-10]

The most common primary underlying disease noted in this study was leukemia, similar to findings in other studies [8,11]. The nature of hematologic malignancy and intensity of myelosuppressive treatment predispose these leukemic patients to develop neutropenia to a higher degree compared to patients with solid tumors [12,13]. Most patients in our study developed febrile neutropenia during the induction phase of chemotherapy, similar to the study of Karanwal [13]. The high incidence of neutropenia with early cycles of chemotherapy may be explained by the high doses of drugs used during induction, while the lower incidence in subsequent cycles is likely due to dose modification and hematopoietic cell adaptation that occur at a later time [14]. The greater degree of myelosuppression during induction may also explain why most patients have positive cultures.

Fever without a focus was most common at the time of presentation in 43.5% of subjects. In both groups of patients, MDI was found in 23.8 % of subjects and most of them belonged to the complicated group. Similarly, high rates of fever without a focus were found by Karanwal in 47%, and Shamsi in 60% of their patients. Taj's report however, showed that this finding was seen in only 18.58% of subjects [15]. A local study involving adult febrile neutropenic patients showed MDI in 27.83% of subjects, close to the frequency of MDI in our study. The study of Padua involving pediatric patients with febrile neutropenia, however, found that CDI (63.8%) was more common than MDI (12.7%)[7]. In our study, bloodstream infection (BSI) was the primary site seen in 53.1% of patients in the severe group. Similar rates of BSI have been documented in other studies [3,15,37]. Of 105 febrile neutropenic patients included in our study, a positive blood culture was seen in 26 patients (24.8%). In other studies, positive cultures were observed in only 7-18% of cases [17,18,19]. The low yield of blood culture in pediatric patients with febrile neutropenia is well-recognized and can be attributed to multiple factors: volume of blood taken, choice of culture media, number of inoculated culture bottles and frequency in performing the procedure [20].

Gram-negative organisms *K. pneumoniae* followed by *E. coli,* were the predominant isolates in

our investigation. Padua's study[7], as well as those done in other countries such as India, Turkey, Brazil, and Japan, reported gram negative bacteria as common isolates in febrile neutropenia patients [13,18,21,22,23]. *E. coli* has been cited as one of the most frequently isolated organisms in other investigations [15,24,25]. Twenty three percent of gram-negative isolates in our study were multi-drug resistant. Manglicmot-Gumboc et. al. noted a similar frequency of gram-negative MDROs occurring in febrile neutropenia patients (20.92%) [6]. A study performed in Italy reported a 13.7% incidence of MDROs associated with bacteremia in their subjects [26]. A study on cancer patients done in Spain showed the following variables to be associated with the acquisition of multidrug resistant gram-negative bacteria: presence of other co-morbidities, antibiotic use in the previous month, urinary catheterization, use of parenteral nutrition, previous intensive care unit admission, mechanical ventilation, previous blood transfusion, and a previous episode of bacteremia. Of these, independent risk factors for developing MDR infection were prior antibiotic exposure and urinary catheterization [26].

In addition to being multi-drug resistant, most of the gram-negative isolates in our study were ESBL-producers. ESBLs are highly diversified enzymes that hydrolyze beta-lactams in the periplasmic space, preventing penicillin-binding. [27] One study on *E. coli* and *K. pneumoniae* bacteremia in patients with neutropenic fever revealed that hospital stay of > 2 weeks within 3 months prior to the onset of bacteremia and use of broad-spectrum cephalosporins 4 weeks prior to the onset of bacteremia were significantly related to the acquisition of ESBL [28].

Three XDROs were documented in our study, a finding that was not seen in earlier studies on febrile neutropenia done in this institution [5,6,7]. A study done by Reddy et al in India showed that extreme drug resistance was seen in 32%, and pan drug resistance in 16% of Gram-negative bacterial infections in their review of sensitivity of bloodstream isolates in children with malignancy [29].

Staphylococcus aureus was the most common gram-positive isolate in our study. Bhatti's study showed that 33.9% of isolates in febrile neutropenic children were gram positive organisms, of which *S. aureus* was the most frequent (9.8%)[30].

Candida organisms were isolated in 16.7% of our patients. In a study in Malaysia, candidemia occurred in 23% of patients [31]. Rates of candidemia varied from 1 to 13.6% in other studies [32,33].

High rates of resistance of isolates to major antimicrobials used in the treatment of febrile neutropenia were evident in this study. *K. pneumoniae* showed high resistance to Ceftazidime (80%), Cefepime (80%), Piperacillin-tazobactam (70%), Meropenem (40%), Gentamicin (50%) and Amikacin (10%). The 2016 Antimicrobial Resistance Surveillance Program (ARSP) reports lower resistance rates to Ceftazidime (13.5%), Cefepime (30.4%), Piperacillin-tazobactam (22.7%), Meropenem (11.4%), Gentamicin (24.0%) and Amikacin (5.5%)[34]. Among the gram-positive organisms, *Staphylococcus aureus* showed 100% resistance to Oxacillin, higher than what was reported by ARSP (61.6%)[34].

Univariate analysis showed that patients with acute myelogenous leukemia, treatment relapse, ANC of ≤ 100 cells/mm3 on admission, fever of >7 days during admission, non-response to empiric antibiotics, MDI, fever without a focus, bloodstream infection, unknown focus of infection, and a positive blood culture were related to severe outcome. Several studies likewise showed AML, fever of more than 5 days, and presence of known isolated organisms, as factors predictive of developing severe outcome on univariate analysis [16,18,35]. There were a few studies which showed profound neutropenia, significant focus of infection, fever of more than 5 days, previous documented infection, and isolation of a known pathogen in cultures [6,18,25] as significant predictive factors associated with severe outcome on multivariate

analysis. Our study, however, showed that the above findings were not significantly associated with a severe outcome on multivariate analysis. Of note was that the studies cited above involved more subjects compared to our investigation. Nevertheless, significant variables found on univariate analysis can still be of value to the clinician to identify those at risk of developing severe outcomes.

CONCLUSIONS

Gram-negative bacteria were the most common pathogens isolated in febrile neutropenic patients. ESBL-producing *K. pneumoniae* was most common followed by *E. coli* and Candida species.

Although results of logistic regression analysis on predictors of severe outcome did not reach statistical significance, Univariate analysis showed that severe outcome was more likely to develop in the presence of the following factors: Acute myelogenous leukemia, treatment relapse, ANC on admission of </= 100 cells/mm3, fever of >7 days during admission, non-response to empiric antibiotics, microbiologically-defined infection, fever without a focus, bloodstream infection, unknown focus of infection and presence of known isolated organisms. These findings can help identify patients at increased risk of developing severe outcome, to promote timely and aggressive medical management and prevent complications and death.

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ORIGINAL ARTICLE

OUTCOME OF CURRENT ANTIBIOTIC REGIMENS USED FOR NEONATAL SEPSIS IN A TERTIARY HOSPITAL

Anne Melva V. Meliton-Ruiz, MD*
Robert Dennis J. Garcia, MD, MHSA*

Makati Medical Center*

Correspondence: Dr. Anne Melva V. Meliton-Ruiz
Email: amvmeliton@gmail.com

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

ABSTRACT

Objective: This paper looked into the outcome of currently used antibiotic regimens for neonatal sepsis in a tertiary hospital.
Methods: This retrospective study reviewed all cases of culture positive neonatal sepsis delivered in a tertiary hospital between January 1, 2000 to December 31, 2015. Demographic profile, stratification as to early-onset and late-onset sepsis, clinical manifestations, culture and antimicrobial susceptibility results, and outcomes were analyzed.
Results: There were 28 cases of culture positive neonatal sepsis reported during the study period, and prematurity and low birth weight were the major risk factors identified. Of these, 8 were early-onset sepsis and 20 were late-onset sepsis cases. Respiratory symptoms were the most common presenting manifestations. Sepsis isolates were evenly distributed between gram-negative bacilli and gram-positive cocci with no ESBL *E. coli* or *Klebsiella pneumoniae* identified. The institution's current empiric antibiotic regimen of cefuroxime and amikacin for early-onset neonatal sepsis was shifted to another drug in 57% of cases. Piperacillin-tazobactam or carbapenem was given for late-onset sepsis. The addition of vancomycin for late-onset sepsis was done where Staphylococcus was considered. Sepsis due to gram-negative bacilli had a high mortality rate.
Conclusion: Our institution's empiric antibiotic regimen which consists of cefuroxime and amikacin for early onset sepsis is effective in 43% of cases. A carbapenem or piperacillin-tazobactam, even without amikacin, proved to be effective for late-onset sepsis. Vancomycin, should be considered for late-onset sepsis, if staphyloccoccal disease is suspected.

KEYWORDS: *neonatal sepsis, antibiotic, neonate, low birth weight*

INTRODUCTION

Neonatal sepsis remains to be a leading cause of morbidity and mortality especially among those delivered in developing countries. An increasing concern in the management of neonatal sepsis is the growing problem of antibiotic resistance in the treatment of these infections. As organisms evolve and acquire resistance to commmonly used antimicrobials, it is important to assess if current empiric antibiotic regimens are still effective against organisms encountered in a particular setting.[1]

At the tertiary hospital studied, Cefuroxime and amikacin have been used since the year 2000 for empiric treatment of early-onset sepsis, and piperacillin-tazobactam for late-onset sepsis. This recommendation was made after analysis of institution-specific blood pathogens showing that group B streptococcus or *Streptococcus agalactiae* was a rare pathogen for early-onset sepsis, contrary to western literature reports. On the other hand, gram negative bacilli, notably *Enterobacter cloacae* and *Klebsiella pneumoniae*, were commonly isolated.[1]

This study looked into the efficacy and outcome of current empiric antibiotic regimens used for neonatal sepsis at a tertiary hospital. Risk factors, presenting symptoms, culture and antimicrobial susceptibility results, and outcomes were likewise analyzed.

MATERIALS AND METHODS

Study Design

This was a retrospective study which looked into cases of neonatal sepsis in a private tertiary hospital, and where bacteremia and/or candidemia were documented by blood culture between January 1, 2000 to December 31, 2015.

Population and Sample Size

Inclusion Criteria

All neonates delivered whose blood culture yielded an isolate interpreted to be a true pathogen, were included. Early-onset sepsis was defined as culture-proven infection occurring in the first seven days of life, while late-onset sepsis referred to cases which occurred on the eighth up to the ninetieth day of life. For very low birth weight (VLBW) neonates (weight < 1500 grams), late-onset sepsis was defined as that which occurred at or more than 72 hours of life.[2]

Exclusion Criteria

Neonates who were admitted but delivered outside the hospital studied (outborn cases), and those with clinical signs of sepsis but whose blood cultures showed no growth, were excluded. Excluded also were cases of sepsis transferred to another hospital, and culture positive cases where blood cultures were positive but isolates were interpreted as contaminants. In cases where blood isolates were positive on two separate occasions, the organisms and antimicrobial susceptibilities were noted.

Data Collection

This study was conducted in accordance with the ethical principles based on the Declaration of Helsinski, WHO guidelines, International Harmonization – Good Clinical Practice, and National Ethics Guidelines for Health Research and approved by the Institutional Review Board (I.R.B.).

The following data were obtained: sex, gestational age, birth weight, manner of delivery, and onset of sepsis defined as the day of the earliest symptom attributable to sepsis.

Risk factors were analyzed which included maternal and neonatal co-morbidities and contraptions present throughout the hospital stay.

Clinical and culture information were collected from the medical records ArchiveOne database, neonatal intensive care unit (N.I.C.U.) census of septic babies, N.I.C.U. audits, and neonatologist and infectious disease specialists' records.

The presence or absence of specific clinical findings were noted. Laboratory findings were recorded before, and on the day that a positive growth was obtained. If a significant isolate was identified, the organism's antimicrobial susceptibilities were recorded. A blood culture growth was considered to be a contaminant if it grew coagulase-negative Staphylococcus (CoNS) and the blood was drawn during the first three days of hospital stay in a neonate with no indwelling intravascular catheter. Specific antibiotic regimens and outcomes of treatment were recorded. A case report form was utilized to organize the data gathered from each case.

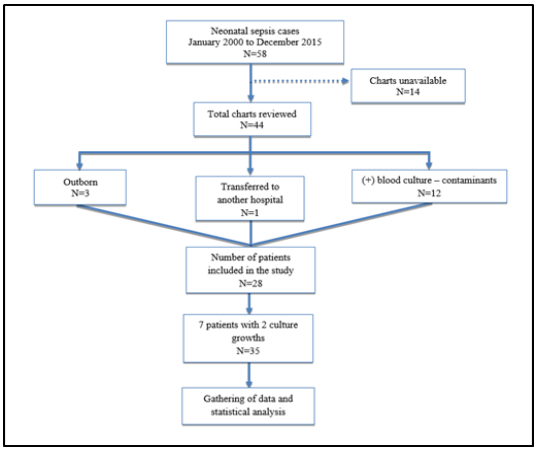

Figure 1. *Methodology Flowchart*

Statistical Analysis

Descriptive statistics using frequencies and percentages were used to analyze the data.

III. RESULTS

There were 58 infants evaluated for sepsis where blood culture grew an organism between January 1, 2000 to December 21, 2015. Fourteen charts (24%) were unavailable or lost in the ArchiveOne database. Among 44 available charts, further exclusions were: outborn (N=3), transferred to another hospital (N=1), and cases where cultures were considered to be contaminants (N=12), yielding a final total of 28 cases. Seven patients had two blood isolates at different times with a total blood isolate of 35. See Figure 1.

The medical records of 28 infants were further reviewed. Of the total cases, 86% were preterms (N=24). Most cases were extremely low birth weight (ELBW, 39%), and VLBW infants (25%). For neonates weighing more than 1,500 grams, there were equal cases of early-onset and late-onset sepsis, while for neonates under 1,500 grams, late-onset sepsis was seen three times more often. Majority of sepsis cases fell under late-onset sepsis (71%). See Table 1.

Table 1. Demographic Data

	Total Number N = 28	% of total N
Gestational Age		
Preterm	24	86%
Term	4	14%
Sex		
Male	16	57%
Female	12	43%
Birth Weight (kg)		
<1	11	39%
1-1.49	7	25%
1.5-2.49	4	14%
>2.5	6	21%
Manner of Delivery		
Spontaneous vaginal delivery	10	36%
Cesarean Section	18	64%
Size for Gestational Age		
Small for GA	10	36%
Appropriate for GA	14	50%
Large for GA	4	14%
Onset of Sepsis		
Early-Onset	**8**	**29%**
>1500g, 0-7 days	5	18%
<1500g, 0-3 days	3	11%
Late-Onset	**20**	**71%**
>1500g, >7 days	5	18%
<1500g, >3 days	15	54%

Maternal urinary tract infection (21%) was the dominant prenatal risk factor for sepsis in the newborn. Neonatal factors that were present among septic neonates were prematurity (86%) and low birth weight (LBW,78%).

Table 2. Factors Associated with Culture-Proven Sepsis in Neonates

	Frequency	Percentage
Prenatal and Perinatal Factors		
Maternal urinary tract infection	6	21%
Meconium-stained amniotic fluid	5	18%
Maternal Fever (≥38)	1	4%
Neonatal Factors		
Prematurity (<37 weeks)	24	86%
Low birth weight	22	79%
Low Apgar score (<6 at 5 min)	1	4%
Contraptions		
N/OGT	20	71%
Umbilical vein catheter	15	54%
Endotracheal tube	12	43%
Intrajugular catheter	1	4%
Chest tube	1	4%

The most common clinical manifestations of septic neonates were tachypnea (68%), desaturation (54%), apnea (43%), and presence of retractions (36%). See Table 3.

Table 3. Clinical Manifestations of Septic Neonates Before Positive Blood Culture

	Frequency	Percentage
Tachypnea	19	68%
Desaturations	15	54%
Apnea	12	43%
Retractions	10	36%
Poor activity	8	29%
Bradycardia	7	25%
Feeding intolerance	6	21%
Poor cry	5	18%
Grunting	3	11%
Blood in nasogastric or orogastric tube aspirate	2	7%
Abdominal distention	1	4%
Abdominal discoloration	1	4%

Table 4 shows that elevated C-reactive protein (CRP,43%) and thrombocytopenia (32%) were the most common laboratory abnormalities identified. Of the nine neonates who had a lumbar tap done, only one had an isolate. Organisms that grew in the endotracheal aspirate were *P. aeruginosa,* CoNS. and *S. aureus* in three cases, which were identical to the bacteria cultured from the blood.

Table 4. Laboratory Abnormalities at Start of Treatment

	Frequency	Percentage
CRP elevation	12	43%
Thrombocytopenia	9	32%
High WBC (above 30)	5	18%
Stool culture positive	5	18%
Endotracheal tube aspirate culture positive	3	11%
Low WBC (below 5)	2	7%
Segmenters>80%	1	4%
CSF culture positive	1	4%

When sepsis cases were divided by timing of onset to early and late-onset, 29% were early, and 71% were late, as seen in Table 5. In early-onset cases, the etiologic organisms were evenly divided between gram-negative bacilli and gram-positive cocci. Among late-onset cases, 52%, 41% and 7% were due to gram-positive cocci, gram-negative bacilli, and candida, respectively.

Table 5. Blood Culture Isolates and Time of Onset

	Early Onset N=8		Late Onset N=27		Total Positive Blood Culture (N=35)	
	Frequency	Percentage	Frequency	Percentage	Total	Percentage
Coagulase-negative Staphylococcus	1	4%	11	41%	12	45%
Staphylococcus aureus	1	4%	3	11%	4	11%
Enterobacter cloacae	0	0%	3	11%	3	9%
Pseudomonas aeruginosa	1	4%	2	7%	3	9%
Serratia marcescens	1	4%	2	7%	3	9%
Candida	0	0%	2	7%	2	6%
Acinetobacter	0	0%	2	7%	2	6%
Klebsiella pneumoniae	1	4%	1	4%	2	6%
Streptococcus viridans	1	4%	0	0%	1	3%
Pseudomonas stutzeri	1	4%	0	0%	1	3%
Streptococcus agalactiae	1	4%	0	0%	1	3%
Enterobacter aerogenes	0	0%	1	4%	1	3%

Among the gram-negative bacilli isolated, only 75% was susceptible to meropenem and 60%

were susceptible to cefuroxime; 100% were susceptible to piperacillin-tazobactam and amikacin, but these two drugs were tested in only six out of fourteen bacterial isolates. All gram-positive bacilli were susceptible to vancomycin. See Table 6.

Table 6. Antibiotic Susceptibility of Clinically Significant Organisms Isolated: % Susceptible

Gram-negatives (N=14)	Frequency	Percentage
Ciprofloxacin	10/10	100%
Cefepime	9/9	100%
Gentamycin	7/7	100%
Piperacillin-Tazobactam	6/6	100%
Amikacin	6/6	100%
Imipenem	4/4	100%
Ceftriaxone	4/4	100%
Ceftazidime	3/3	100%
Meropenem	3/4	75%
Cefuroxime	3/5	60%

Gram-positive cocci (N=18)	Frequency	Percentage
Vancomycin	14/14	100%
Linezolid	6/6	100%
Ciprofloxacin	3/3	100%
Gentamycin	2/2	100%
Clindamycin	6/10	60%
Oxacillin	6/16	38%

Figure 2 shows the antibiotics used among eight cases of early-onset sepsis. The first-line antibiotic regimen of cefuroxime and amikacin was used in most (88%) cases. Among those given cefuroxime and amikacin, amikacin was continued up until the end of treatment, but cefuroxime was shifted in 57% of cases. The treatment regimen of one neonate who was started on ampicillin and amikacin, was shifted to meropenem. At the end of treatment for the eight cases of early-onset sepsis, all were on amikacin, three were on cefuroxime, two each were on a carbapenem or a third-generation cephalosporin, and one was on piperacillin-tazobactam.

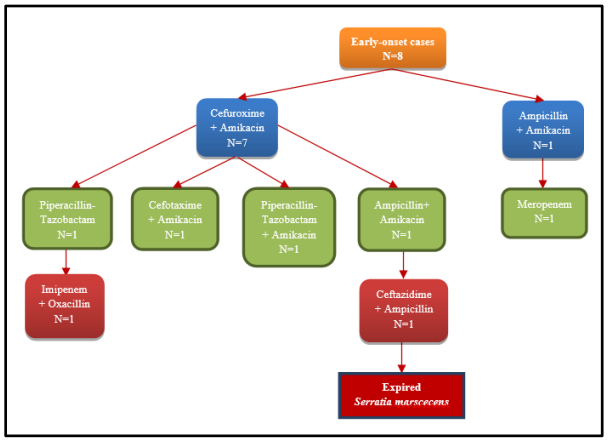

Figure 2. *Initial antibiotic choices and subsequent changes during the course of early-onset sepsis. Orange: Total early-onset cases (N=8); Blue: Antibiotic regimen initiated; Green: First shift of regimen; Red: Second shift of regimen*

Figure 3 shows the antibiotic usage pattern among twenty cases of late-onset sepsis. Initial regimen showed that piperacillin-tazobacatam was used in 70%, amikacin in 65%, and meropenem in 10%. Among the 14 cases started on piperacillin-tazobactam, two (14%) were given the drug up to the end of treatment while in the remaining twelve (86%), piperacillin-tazobacatam was shifted to a carbapenem in 67%. At the end of treatment for 20 cases of late-onset sepsis, 50% were on a carbapenem, 30% on vancomycin, 25% on fluconazole, and 10% on piperacillin-tazobactam.

Figure 3: *Initial antibiotic choices and subsequent changes during the course of late-onset sepsis. Green: Total late-onset cases (N=20); Blue: Antibiotic regimen initiated; Violet: First shift of regimen; Orange: Second shift of regimen; Red: Expired cases.*

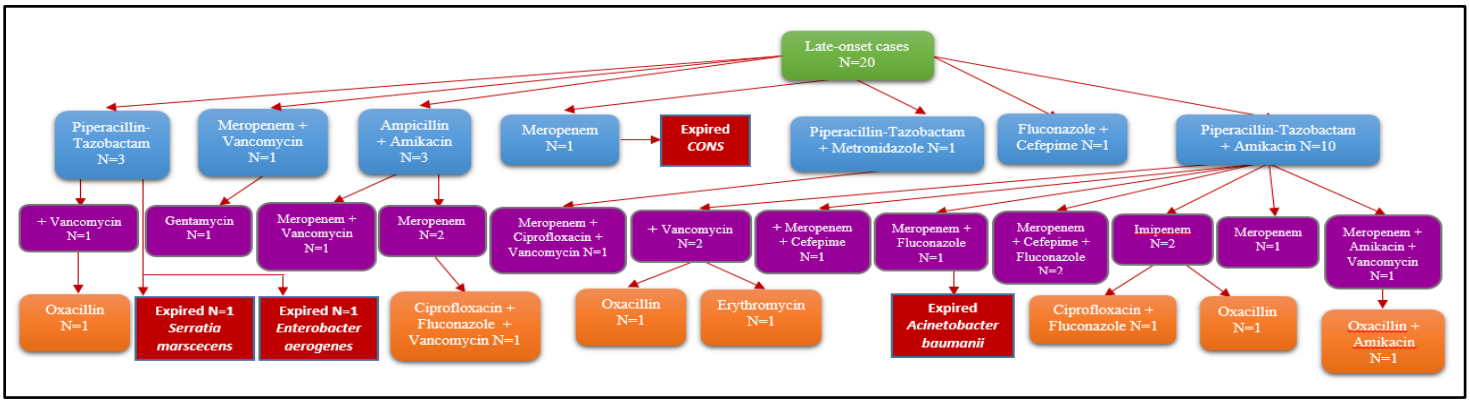

Table 7 shows that 20% of gram-negative bacterial infections and 6% of gram positive sepsis died. Two cases with candidemia survived.

There were six mortalities, with five due to gram-negative bacilli septicemia. One infant with late-onset CoNS died due to severe hyaline membrane disease.

Table 7. Summary Table of Outcomes

	Length of Stay (days)	Length of Treatment (days)	Pneumonia	Low platelet count	Bleed	NEC	Meningitis	Osteomyelitis	Septic Arthritis	Well	Died
Gram-Negative	60.2	13.4	7%	27%	7%	7%	7%	0	0	80%	20%
Gram-Positive	58.1	14.7	17%	6%	0	0	0	6%	6%	94%	6%
Candida	91.5	18.5	0	0	50%	50%	0	0	0	100%	0

IV. DISCUSSION

This study found that 86% of sepsis cases were in preterm neonates of which 25% were VLBW and 39% were ELBW This supports a similar study done which looked into five-hospitals in Manila, Cebu, Baguio and Davao and cases of neonatal sepsis with blood culture growths where 29-65% were preterms.[3] At Philippine General Hospital (PGH), a study on 103 neonates with blood culture growths, found that 66% were premature, 36% were L.B.W., and 7% were ELBW.[4]

In another study in PGH involving 17 culture-proven cases, 65% were preterms.[5] Presence of VLBW is a known independent risk for neonatal sepsis.[6]

The most common clinical manifestations were respiratory in nature. Mayuga reported that among 17 neonatal sepsis cases at PGH, 71% showed respiratory manifestations.[5] Among 63 neonates with *Serratia marcescens* bacteremia at Baguio General Hospital, presenting signs and symptoms were respiratory distress (51%), poor suck (25%) and bleeding (22%).[7]

The most common laboratory abnormalities seen at the start of treatment were an elevated CRP (43%) and thrombocytopenia (32%). Such indicators of bacteremia are of value while awaiting blood culture results since not all patients will present with frank signs of sepsis. In a study in PGH, bacteremic neonates had an odds ratio of 4.7 to be thrombocytopenic; sensitivity of thrombocytopenia for bacteremia was low at 35%, and negative predictive value (NPV) was 87%.[8] In a review of various quantitative CRP tests used in neonatal sepsis, Da Silva found that CRP is probably the best diagnostic test to evaluate neonatal sepsis; sensitivity was 58-100%, and NPV was 86-100%.[9]

Of nine neonates where a lumbar tap was done, only one had a growth. Among 103 septic neonates at PGH where 93% grew gram-negative bacilli in the blood, there was no documented case of meningitis.[5] Among 289 blood culture-positive neonates from five local hospitals, only 1.4% had meningitis.[5] These data indicate low rates of meningitis occurring with bacteremia.

In this study, among eight neonates with early-onset sepsis, the etiologic organisms were evenly distributed between gram-negative bacilli and gram-positive cocci. Among 139 neonates with blood culture-positive sepsis from five local hospitals, the most common organisms were Pseudomonas spp. (43%), Burkholderia spp. (22%), Klebsiella spp. (11%), Acinetobacter spp. (5%), and Enterobacter (4%) spp. and *S. epidermidis* (4%); 88% of the isolates came from PGH. For the four other hospitals, there were 17 blood culture growths, and the organisms were Enterobacter spp. (24%), Klebsiella spp. (24%), Pseudomonas spp. (18%), E. coli (12%), and Aeromonas spp., Salmonella spp., *S. epidermidis*, and Candida spp. (6% each). There was not a single growth of *Streptococcus agalactiae* in the study[3] contrary to studies in the U.S. where up to 46% of early-onset sepsis are due to *S. agalactiae*.[10]

Among 108 bacteremic neonates at Cebu Doctors' University Hospital (2005-2008), Staphylococcus spp. (30%), Enterobacter spp. (23%), Klebsiella spp, (13%), Streptococcus spp. (9%), E. coli

(7%), Acinetobacter spp. (6%) and Enterococcus spp. (5%) were the most common isolates.[11]

Among 20 neonates with late-onset sepsis, 52% were due to gram-positive cocci, 41% were due to gram-negative bacilli, while 7% were due to candida. There is no published local study that distinguishes pathogens seen in early-onset vs late-onset sepsis.

Still at the NICU of the study hospital, there were three studies conducted (unpublished) on the most common organisms isolated from blood cultures among neonates evaluated for sepsis. Disregarding the CoNS growths which were generally regarded as contaminants, the top four isolates were Enterobacter spp., Klebsiella spp., Pseudomonas spp. and Acinetobacter spp. *Streptococcus agalactiae* was isolated in three neonates (2%) over the 10-year period.[1 12 13] Together with the local data cited above, it appears that S. agalactiae is an infrequent pathogen in neonatal sepsis in the Philippines.

For the gram-negative bacilli in the study, 75% were susceptible to meropenem and 60% were susceptible to cefuroxime; 100% were susceptible to piperacillin-tazobactam and amikacin. All gram-positive cocci were susceptible to vancomycin. The antibiogram results cannot be generalized however, since testing is automated and the list of antimicrobials tested is specific and limited. For example, *P. aeruginosa* or *B. cepacia* are not inherently susceptible to cefuroxime, hence, testing is not done.

Among early-onset sepsis cases, the first-line antibiotic regimen of cefuroxime and amikacin was used in 88% of cases. This regimen has been used at the tertiary hospital studied since 1999 on the basis of two unpublished studies using blood culture growths from the institution and their antimicrobial susceptibilities.[1 12] In this study, among those given cefuroxime and amikacin, amikacin was continued for all, but cefuroxime was shifted to another antibiotic in 57% of cases. At end of treatment for early-onset sepsis, all eight neonates received 3 to 7 days of amikacin, three were on cefuroxime, two were on a carbapenem, two were on a third-generation cephalosporin, and one was on piperacillin-tazobactam. In a local study involving five-hospitals, four institutions used ampicillin and an aminoglycoside for empiric treatment of neonatal sepsis; however, the success rates of ampicillin and gentamicin were only 48% for the sepsis cases, including those who were culture-negative. The authors suggested that the regimen of ampicillin and aminoglycoside was less useful in the participating hospitals, based on antimicrobial resistance rates and the outcomes seen.[3]

Among twenty cases of late-onset sepsis, the initial regimen consisted of piperacillin-tazobacatam in 70%, amikacin in 65%, and meropenem in 10%. Among 14 patients started on piperacillin-tazobactam, only two (14%) remained on this drug up to the end of treatment; in the other twelve (86%), piperacillin-tazobacatam was replaced with a carbapenem in nine (75%). At the end of treatment for the 20 infants with late-onset sepsis, 50% were on a carbapenem, 30% on vancomycin, 25% on fluconazole and 10% on piperacillin-tazobactam. These results imply that carbapenems may be more effective than piperacillin-tazobactam for the organisms encountered in the unit, but this finding is inconclusive given the retrospective nature of the study.

There were two neonates with candidemia, a known risk with the use of very broad-spectrum antimicrobials. Use of very broad-spectrum antimicrobials like carbapenems and piperacillin-tazobactam is common in the N.I.C.U. due to high resistance rates to third generation cephalosporins. Among 25 neonates with Enterobacter spp. bacteremia at Cebu Doctors' Hospital, 60% of the isolates were resistant to cefotaxime and

ceftazidime.[11] Among 34 neonates treated for sepsis in Baguio (31% of whom were bacteremic) with 70% of bacteremia due to Enterobacter spp., meropenem was used for all, with a favorable outcome in 84% and a mortality rate of 6%.[14] Piperacillin-tazobactam, in combination with an aminoglycoside, was used in PGH among 57 children with culture-proven infections, 63% of whom were neonates. This was done because of high rates of cephalosporin resistance. The favorable response rate was 79%, with no deaths occurring while on piperacillin-tazobactam.[15]

The results showed no sepsis-attributable mortality to CoNS or *Staphylococcus aureus*. The addition of vancomycin should be considered in late-onset sepsis as 50% of early onset sepsis and 52% of late onset sepsis respectively are due to these two organisms.

This study revealed that in spite of over 17 years of empiric use of cefuroxime and amikacin for early onset-sepsis, and a choice of piperacillin-tazobactam or a carbapenem for late-onset sepsis, there was not a single case of extended-spectrum-beta-lactamase-producing (ESBL) *E. coli or K. pneumoniae* among the blood isolates.

Even as data in Figure 2 and Table 6 indicate that the combination of cefuroxime and amikacin will not cover all potential pathogens in cases of early-onset sepsis, it remains to be seen if a stronger empiric first-line regimen (e.g., third generation cephalosporin) will be recommended, because of the risks of the emergence of ESBL strains of gram-negative bacilli. Third-generation cephalosporin use is a known risk for the emergence of ESBL strains in an intensive care unit.[16] At the institution studied, the hospital-wide (year 2015) ESBL rates for *K. pneumoniae* and *E. coli* were 16.8% and 21.5% respectively, but these growths have been mostly confined to the adult service intensive care areas.[17]

Twenty percent of gram-negative sepsis and 6% of gram-positive bacteremia cases died. Among 289 blood culture-positive neonates from five local hospitals, overall mortality was 11%.[3] Among 63 neonates with *Serratia marcescens* bacteremia at Baguio General Hospital, case fatality rate was 29%.[7] Among 25 neonates with Enterobacter spp. bacteremia in Cebu Doctors' Hospital, overall mortality rate was 56%.[3]

Organisms causing neonatal sepsis were roughly evenly divided between gram-negative bacilli and gram-positive cocci, but gram-negative bacilli caused a higher mortality rate (20% vs. 6%). The current antibiotic regimen of cefuroxime and amikacin for early-onset neonatal sepsis was changed in 57% of cases, indicating that a constant re-evaluation of any regimen is necessary to determine if change in the treatment is needed. Although piperacillin-tazobactam has been favored for late-onset sepsis in the studied unit in the last 15 years, more septic neonates ended treatment with a carbapenem. The addition of vancomycin in the treatment of late-onset sepsis should be considered.

V. CONCLUSION

In our tertiary hospital, cefuroxime and amikacin are effective for early-onset sepsis in 43% of cases. For late-onset sepsis, a carbapenem or piperacillin-tazobactam are recommended. There was a mortality rate of 20% and 6% among gram-positive and gram-negative bacteria with the current regimen. The antibiotic of choice should be decided upon by the clinician based on current recommendations, with consideration for maternal and neonatal risk factors, including clinical manifestations and laboratory abnormalities.

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Tuberculosis Verrucosa Cutis in an 11-year-old girl: A Case Report

CASE REPORT

Tuberculosis Verrucosa Cutis in an 11-year-old girl A Case Report

Maria Vinna N. Crisostomo, MD*
Karen Lee P. Alabado, MD*
Maricarr Pamela M. Lacuesta-Gutierrez, MD*

*Southern Philippines Medical Center

Correspondence:
Dr. Maria Vinna N. Crisostomo
Email:
docmavie_crisostomo@yahoo.com

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

ABSTRACT

We report a case of an 11-year-old girl who presented with a gradually enlarging verrucous plaque on the left knee for 3 years. Physical examination showed a solitary, slightly erythematous, scaly, verrucous plaque on the left knee measuring about 1.5 cm x 2 cm. Biopsy revealed granulomatous dermatitis consistent with cutaneous tuberculosis. A diagnosis of tuberculosis verrucosa cutis (TBVC) was made and anti-tuberculous therapy was initiated consisting of rifampicin, isoniazid, pyrazinamide and ethambutol for 2 months followed by rifampicin and isoniazid for 4 months. Upon completion of therapy, only a slightly atrophic scar remained, supporting our diagnosis. This report highlights TBVC must be considered in patients with chronic skin lesions in countries with high prevalence of tuberculosis.

KEYWORDS: *tuberculosis verrucosa cutis, cutaneous tuberculosis, anti-tuberculosis therapy*

INTRODUCTION

Tuberculosis is a global problem. There is an estimated 10.4 million new cases of tuberculosis worldwide, extrapulmonary cases accounting for 15% of the global burden.[1]

Cutaneous tuberculosis is an uncommon manifestation of *Mycobacterium tuberculosis* infection. In the absence of high degree of suspicion, it often poses a diagnostic dilemma to an unsuspecting clinician and may result in delayed diagnosis and treatment.[2,3]

CASE REPORT

This is a case of an 11 year-old girl who presented with a gradually enlarging verrucous plaque on the left knee. The lesion started as a solitary, slightly erythematous papule that was noted few days after sustaining a minor injury. She noted gradual peripheral expansion of the lesion associated with occasional mild pruritus in the span of three years. She denies cough, night sweats, weight loss and other constitutional signs and symptoms. No consults were done, nor medications applied or taken.

Her past medical history was unremarkable and there were no previous hospitalizations. The patient's grandfather was previously treated for pulmonary tuberculosis. The patient had completed her vaccination including BCG vaccine at a local health center. She is the second in a family composed of 4 children and is a student with good academic standing. She lives in a rural community in Davao del Sur.

Physical examination upon consult in our center revealed a solitary, slightly erythematous, scaly, verrucous plaque on the left knee measuring about 1.5 cm x 2 cm (Figure 1a). Diascopy of the lesion did not show an apple-jelly color. There was neither regional lymphadenopathy nor other significant systemic abnormalities noted.

Our initial impression at the dermatology clinic was tuberculosis verrucosa cutis (TBVC) and we immediately requested for laboratory workup to support our diagnosis. The patient was given mild emollients while awaiting the results of the tests done.

Complete blood count and urinalysis were normal. Chest radiography revealed hazy infiltrates in the lower and middle lung fields and retrocardiac spaces. Sputum examination was negative for acid-fast bacilli. Tuberculin skin test was positive (20mm) after 48hrs.

Hematoxylin and eosin stained sections prepared from the punch biopsy of the lesion showed orthokeratosis with focal parakeratosis; focal hyperplasia and spongiosis of the epidermis; presence of dense inflammatory infiltrates in the upper dermis; and granulomatous foci with rare multinucleated giant cells in the mid-dermis. The histopathological diagnosis was granulomatous and suppurative dermatitis.

We were unable to confirm the presence of M. tuberculosis through mycobacterial culture because of unavailability of this test in our institution or through polymerase chain reaction (PCR) because of its high cost.

In view of the clinical presentation and histopathologic findings, the patient was classified as extrapulmonary tuberculosis, clinically-diagnosed based on country guidelines on the diagnosis and treatment of tuberculosis.[4] Standard anti-tuberculosis therapy was initiated under directly observed short course therapy (DOTS). She was given fixed-dose combination of isoniazid, pyrazinamide, rifampicin and ethambutol for two months during the intensive phase; followed by isoniazid and rifampicin for 4 months during the maintenance phase. No adverse events were observed during the course of treatment. Complete regression of the lesion was noted after completion of therapy leaving a slightly atrophic scar (Figure 1b and 1c).

DISCUSSION

Cutaneous tuberculosis is uncommon and makes up a very small proportion of extrapulmonary

tuberculosis cases.[5] According to the World Health Organization (WHO), there are 10.4 million people infected with tuberculosis worldwide, 10% of which are seen in children.[1] Local data shows that there are 70 cases of tuberculosis involving skin and subcutaneous tissue out of the 2,100 cases of tuberculosis among pediatric population as reported by the accredited hospitals of the Philippine Pediatric Society.[6] In our institution, there were 4 cases of cutaneous tuberculosis both in adults and pediatric patients reported in the past 3 years.

The causative agent of cutaneous tuberculosis is *Mycobacterium tuberculosis*. Its clinical presentation is varied and may mimic other skin infections. Lesions may vary from papules to plaques, nodules and ulcers. Therefore, cutaneous tuberculosis should be considered in patients with chronic skin lesions that do not improve with adequate management for other eczematous lesions.[2-3,7-10]

There are 4 major categories of cutaneous tuberculosis based on the route of infection: (1) direct inoculation from an exogenous source such as in tuberculous chancre and tuberculosis verrucosa cutis; (2) direct extension from a preexisting primary focus such as in orificial tuberculosis and scrofuloderma; (3) hematogenous spread such as in miliary tuberculosis, tuberculous gumma and lupus vulgaris; and (4) lymphatic spread such as in lupus vulgaris.[3,9]

TBVC is a paucibacillary tuberculosis that is acquired through direct inoculation following a minor skin injury in a patient with moderate to strong immunity.[3,5,7-9] Presence of moderate to strong immunity evidenced by positive tuberculin skin test and history of BCG vaccination contributed to disease presentation in our patient. In a study by Kumar and colleagues, positivity to tuberculin skin test and a history of BCG vaccination is more common in patients with localized disease which denotes sensitization to the organism either due to the presence of the disease, exposure to other related environmental mycobacteria, from exposure to infected close contact with M. tuberculosis or BCG vaccination.[11]

However, a negative tuberculin skin test demonstrating low immunity does not exclude the diagnosis of TBVC. [8]

In children, the sites of predilection are the knee, thighs, buttocks and hands.[2,3,8,9,12] Lesions of TBVC usually starts as an asymptomatic papule which gradually enlarges to become a verrucous plaque.[2,7-9] The same was observed in our patient's lesion that started as an asymptomatic papule and slowly enlarged in the span of three years. It may be mistaken for psoriasis, lichen simplex chronicus, atypical mycobacterial infections, and other chronic skin conditions. [7] The positive tuberculin skin test in this patient demonstrates the presence of immunity to the bacilli. In endemic areas like our country, the Philippines, the bacilli may be present in the environment and children may acquire the infection while playing in contaminated ground. [7-8]

Diagnosis of cutaneous tuberculosis is based on clinical features, tuberculin skin test, interferon-gamma release assays, histopathology, culture, and polymerase chain reaction.[10] The gold standard for diagnosis remains to be mycobacterial culture, however, the yield is low especially for paucibacillary variants such as TBVC. [10] Polymerase chain reaction is useful in confirming the presence of AFB but has positivity rate of only 55% in TBVC.[2] These methods complement the clinico-histopathologic diagnosis and increases diagnostic accuracy, but are often unavailable and expensive in high burden areas of tuberculosis.[2,10,13] As in this patient's case, PCR was not done due to its high cost while culture was unavailable at our institution.

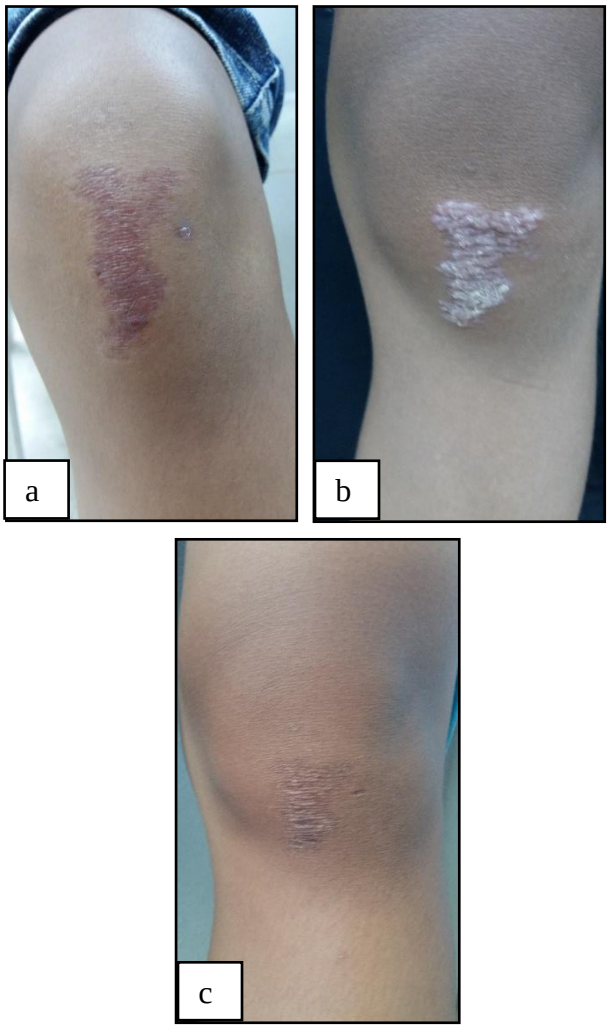

***Figure 1**. A solitary, erythematous, scaly, verrucous plaque on the left knee measuring 1.5 x 2cm prior to initiation of anti-tuberculous therapy (a). Follow-up after 2 months of therapy with noted flattening of the plaque (b). Follow-up after 6 months with noted complete resolution leaving an atrophic scar (c).*

Verrucous plaques with horny surface and deep clefts affecting the lower limbs were the characteristic features seen in our patient. Histologically, cutaneous tuberculosis has predominance of lymphocytes and presence of epithelioid granulomas and multinucleated giant cells.[2,10] Specifically, in TBVC, there is the presence of hyperkeratosis and acanthosis of the epidermis.[2,10] These changes were consistent with the histological findings in our patient. With a strong clinical suspicion and histological findings consistent with TBVC our patient was started on anti-tuberculosis regimen.

The recommendation of the National Tuberculosis Control Program in the treatment of newly-diagnosed tuberculosis involving the skin whether bacteriologically confirmed or clinically-diagnosed is 2 months of isoniazid (10 mkd), rifampicin (15 mkd), pyrazinamide (30 mkd) and ethambutol (20 mkd) followed by 4 months of isoniazid and rifampicin.[4] In this patient, significant regression of the lesion was seen after 2 months of intensive therapy and complete regression by the end of 6 months was noted. There were no untoward side effects reported throughout the course of therapy.

Therapeutic response has been used as a diagnostic criterion in the diagnosis of cutaneous tuberculosis.[2,3,10,13] Ramam et al recommends 4 weeks (with extension of 2 weeks) of therapeutic trial with anti-tuberculosis therapy to prove the diagnosis of cutaneous tuberculosis.[13] In non-responsive patients, other diagnosis such as atypical mycobacterial infections, deep fungal infections, cutaneous leishmaniasis and other granulomatous conditions should be considered. But with the increasing number of multi-drug resistant tuberculosis (MDR-TB), even in children, MDR-TB should also be considered in patients with inadequate response to first-line anti-tuberculosis drugs.[14] In this case, there was noted flattening of the lesions within four weeks of first-line anti-tuberculosis therapy, supporting our diagnosis.

Although we were unable to demonstrate the presence of AFB in the lesion, our clinical findings, positive tuberculin test, histopathological findings and excellent response to anti-tuberculosis treatment support our diagnosis of TBVC.

The clinical presentation, management and response to treatment of our case are similar to those reported in literature. Janjua and colleagues reported a case of TBVC presenting as an annular plaque on the knee in a 15-year-old girl who showed

good response with daily anti-tuberculosis therapy within 3 months and was treated until 6 months.[7] Similarly, Casimiro and colleagues reported a case of verrucous plaque on the thigh which also showed excellent response with therapy. In contrast to this case, both were able to perform culture studies and document the presence of *Mycobacterium tuberculosis* in the lesion.

Aside from anti-tuberculosis therapy, surgical management maybe an option for some cases of TBVC not responsive to conventional medical therapy.[15] There are no topical regimens available for TBVC and other forms of cutaneous tuberculosis.[16]

Majority of children with cutaneous tuberculosis belong to a low socioeconomic status.[3] Lesions of cutaneous tuberculosis including TBVC are often unsightly and poses a cosmetic concern for patients. Such is the case of our patient who was significantly bothered by the presence of verrucous lesions on her knees. Although spontaneous regression can occur in cases of TBVC, delay in treatment may result to persistence and progression of lesion leading to deformities. Systemic organ involvement may occur in other forms of cutaneous tuberculosis such as lupus vulgaris and scrofuloderma.[11]

Awareness and early diagnosis of TBVC and other forms of cutaneous tuberculosis is critical in early management and treatment. Every physician should have a high degree of suspicion in diagnosing cutaneous tuberculosis, especially in highly endemic areas.

ACKNOWLEDGMENTS

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An informed consent/assent was obtained from the patient for the publication of this case.

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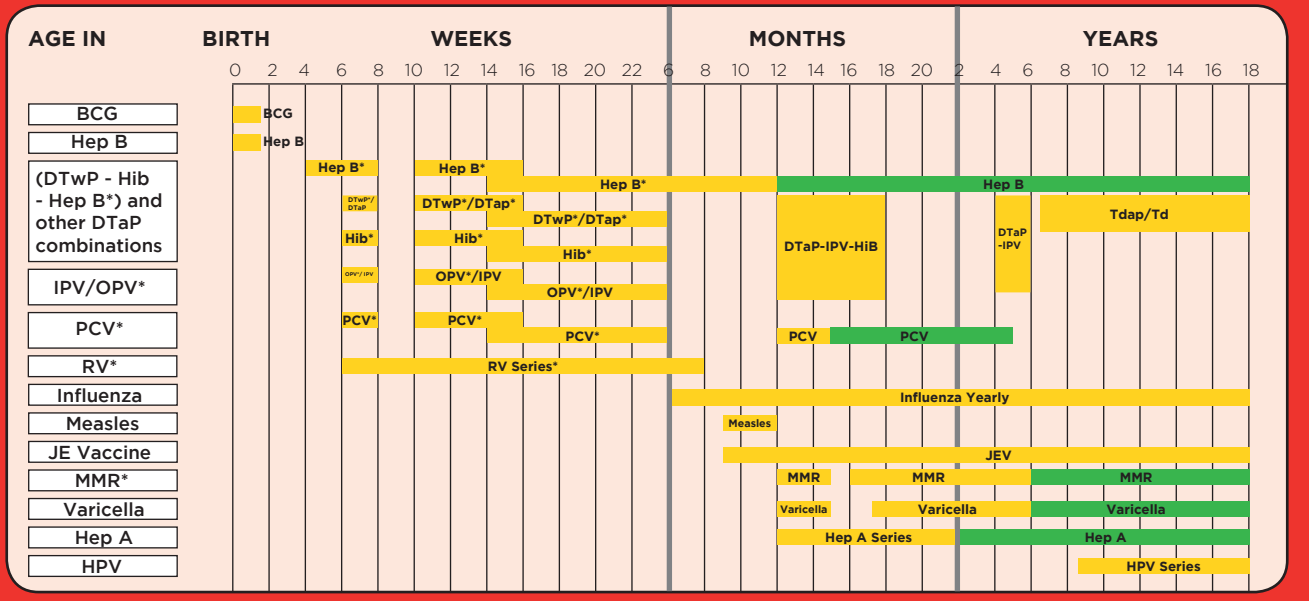
Childhood Immunization Schedule 2018



DISCLAIMER:
The Childhood Immunization Schedule presents recommendations for immunization for children and adolescents based on updated literature review, experience and premises current at the time of publication. The PPS, PIDSP and PFV acknowledge that individual circumstances may warrant a decision differing from the recommendations given here. Physicians must regularly update their knowledge about specific vaccines and their use because information about safety and efficacy of vaccines and recommendations relative to their administration continue to develop after a vaccine is licensed.

Vaccines in the Philippine National Immunization Program (NIP)
The following vaccines are in the 2018 NIP:
• BCG, monovalent Hep B, Pentavalent vaccine (DTwP-Hib-HepB), bivalent OPV, IPV, PCV, MMR, MR, Td and HPV.

Recommended Vaccines
These are vaccines not included in the NIP which are recommended by the Philippines Pediatric Society (PPS), Pediatric Infectious Disease Society of the Philippines (PIDSP) and the Philippine Foundation for Vaccination (PFV).

ANNOTATIONS

Bacille Calmette-Guérin (BCG)
- Given intradermally (ID)
- The dose of BCG is 0.05 ml for children < 12 months of age and 0.1 ml for children > 12 months of age
- Given at the earliest possible age after birth preferably within the first 2 months of life
- For healthy infants and children > 2 months who were not given BCG at birth, PPD prior to BCG vaccination is not necessary. However, PPD is recommended prior to BCG vaccination if any of the following is present:
  – Congenital TB
  – History of close contact to known or suspected infectious TB cases
  – Clinical findings suggestive of TB and/or chest x-ray suggestive of TB

In the presence of any of these conditions, an induration of ≥ 5mm is considered positive and BCG is no longer recommended.

Hepatitis B Vaccine (HBV)
- Given intramuscularly (IM)
- Administer the first dose of monovalent HBV to all newborns >2kgs within 24 hours of life.
- A 2nd dose is given 1-2 months after the birth dose
- The final dose is administered not earlier than 24 weeks of age. Another dose is needed if the last dose was given at age <24 weeks.

For infants born to HBsAg (+) mothers:
- Administer HBV and HBIG (0.5ml) within 12 hours of life. HBIG should be administered not later than 7 days of age if not immediately available.

For infants born to mothers with unknown HBsAg status:
- with birth weight >2kgs, administer HBV within 12 hours of birth and determine the mother's HBsAg as soon as possible. If HBsAg (+), administer also HBIG not later than 7 days of age.
- with birth weight <2kgs, administer HBIG in addition to HBV within 12 hours of life.

For preterm infants:
- If born to HBsAg (-) mothers and medically stable, the 1st dose of HBV maybe given at 30 days of chronological age regardless of weight, and this can be counted as part of the 3-dose primary series.
- For those <2 kgs, the 1st dose received at birth is not counted as part of the vaccine series. Additional 3 HBV doses are needed.

Haemophilus influenzae Type b Conjugate Vaccine (Hib)
- Given intramuscularly (IM)
- Given as a 3-dose primary series with a minimum age of 6 weeks and a minimum interval of 4 weeks
- A booster dose is given between 12-15 months of age with an interval of 6 months from the 3rd dose
  Refer to Vaccines for Special Groups for Hib recommendation in high risk children

Diphtheria and Tetanus Toxoid and Pertussis Vaccine (DTP)
- Given intramuscularly (IM)
- Given at a minimum age of 6 weeks with a minimum interval of 4 weeks
- Complete a 5-dose series at ages 2, 4, 6, 15 through 18 months, and 4 through 6 years. The recommended interval between the 3rd and 4th dose is 6 months, but a minimum interval of 4 months is valid
- The 5th dose of DTaP vaccine may not be given if the 4th dose was administered at age 4 years or older.

Inactivated Poliovirus Vaccine (IPV)
- Given intramuscularly (IM)
- Usually given in combination with DTaP and Hib, with or without Hep B
- Given at a minimum age of 6 weeks with a minimum interval of 4 weeks
- The primary series consists of 3 doses
- A booster dose should be given on or after the 4th birthday and at least 6 months from the previous dose

Rotavirus Vaccine (RV)
- Given per orem (PO)
- Given at a minimum age of 6 weeks with a minimum interval of 4 weeks between doses. The last dose should be administered not later than 32 weeks of age.
- The monovalent human rotavirus vaccine (RV1) is given as a 2-dose series and the pentavalent human bovine rotavirus vaccine (RV5) is given as a 3-dose series.

Pneumococcal Conjugate Vaccines (PCV)
- Given intramuscularly (IM)
- Given at a minimum age of 6 weeks for PCV10 and PCV 13
- Primary vaccination consists of 3 doses with an interval of at least 4 weeks between doses plus a booster dose given 6 months after the 3rd dose.
- Healthy children 2 to 5 years old who do not have previous PCV vaccination may be given 1 dose of PCV 13, or 2 doses of PCV 10 at least 8 weeks apart

Refer to Vaccines for Special Groups for Pneumococcal Vaccine recommendation in high-risk children.

Influenza Vaccine (Trivalent/Quadrivalent Influenza Vaccine)
- Trivalent influenza vaccine (TIV) given intramuscularly (IM) or subcutaneously (SC)
- Quadrivalent influenza vaccine (QIV) given intramuscularly (IM)
- Given at a minimum age of 6 months
- The dose of influenza vaccine is 0.25 ml for children 6 months to 35 months and 0.5 ml for children 36 months to 18 years
- Children 6 months to 8 years receiving influenza vaccine for the 1st time should receive 2 doses separated by at least 4 weeks
- If only one dose was given during the previous influenza season, give 2 doses of the vaccine then one dose yearly thereafter
- Children aged 9 to 18 years should receive one dose of the vaccine yearly
- Annual vaccination should begin in February but may be given throughout the year

Measles Vaccine
- Given subcutaneously (SC)
- Given at the age of 9 months, but may be given as early as 6 months of age in cases of outbreaks as declared by public health authorities
- If monovalent measles is not available, MMR may be given

Japanese Encephalitis Vaccine (JE)
- Given subcutaneously (SC)
- Given at a minimum age of 9 months
- Children 9 months to 17 years of age should receive one primary dose followed by a booster dose 12-24 months after the primary dose
- Individuals 18 years and older should receive a single dose only

Measles-Mumps-Rubella (MMR) Vaccine
- Given subcutaneously (SC)
- Given at a minimum age of 12 months
- 2 doses of MMR vaccine are recommended
- The 2nd dose is usually given from 4-6 years of age but may be given at an earlier age with a minimum of 4 weeks interval between doses.

Varicella Vaccine
- Given subcutaneously (SC)
- Given at a minimum age of 12 months
- 2 doses of varicella vaccine are recommended
- The 2nd dose is usually given at 4-6 years of age, but may be given earlier at an interval of 3 months from the first dose.
- If the 2nd dose was given 4 weeks from the first dose, it is considered valid.
- For children 13 years and above, the recommended minimum interval between doses is 4 weeks.

Hepatitis A Vaccine (HAV)
- Given intramuscularly (IM)
- Given at a minimum age of 12 months
- 2 doses of the vaccine are recommended
- The 2nd dose is given at least 6 months from the 1st dose

Measles-Mumps-Rubella-Varicella Vaccine (MMRV)
- Given subcutaneously (SC)
- Given at a minimum age of 12 months
- MMRV may be given as an alternative to separately administered MMR and Varicella vaccines
- The maximum age is 12 years
- The recommended minimum interval between doses is 3 months

Human Papillomavirus Vaccine (HPV)
- Given intramuscularly (IM)
- For ages 9-14 years, a 2-dose series is recommended
  – Bivalent HPV (2vHPV), quadrivalent (4vHPV) or nonavalent (9vHPV) given at 0 and 6 months
  – If the interval between the 1st and 2nd dose is less than 6 months a 3rd dose is needed. The minimum interval between the 2nd and 3rd dose is 3 months.
- For ages 15 years and older, a 3-dose series is recommended,.
  – Bivalent HPV (2vHPV), quadrivalent (4vHPV) or nonavalent (9vHPV) at 0, 2 and 6 months.
  – The minimum interval between the 1st and the 2nd dose is 1 month and the minimum interval between the 2nd and 3rd dose is 3 months. The 3rd dose should be given at least 6months from the 1st dose.

For males 9-18 years of age, a 4vHPV and 9vHPV can be given for the prevention of anogenital warts and anal cancer

Tetanus and Diphtheria Toxoid (Td)/ Tetanus and Diphtheria Toxoid and Acellular Pertussis Vaccine (TdaP)
- Given intramuscularly (IM)
- For children who are fully immunized, Td booster doses should be given every 10 years.
- For children aged > 7 years old, a single dose of Tdap can be given and can replace due Td. It can be administered regardless of the interval since the last tetanus and diphtheria toxoid containing vaccine. Subsequent doses are given as Td

*Fully immunized is defined as 5 doses of DTP or 4 doses of DTP if the 4th dose was given on or after the 4th birthday

For pregnant adolescents
- Fully immunized:
  – administer 1 dose of Tdap vaccine during 27 to 36 wks AOG regardless of previous Td or Tdap vaccination
- Unimmunized:
  – administer a 3 dose tetanus-diphtheria containing vaccine (Td) following a 0-1-6 month schedule. Tdap should replace one dose of Td given during 27 to 36 wks AOG

ANNOTATIONS: VACCINES FOR HIGH RISKS / SPECIAL GROUPS 2018

Pneumococcal Conjugate Vaccine (PCV)/ Pneumococcal Polysaccharide Vaccine (PPSV23)

- Given intramuscularly (IM)
  - All recommended PCV doses should be given prior to PPSV23 if possible. The two vaccines should not be co-administered. If a dose of PPSV23 is inadvertently given earlier than the recommended interval, the dose need not be repeated.
  - The following tables summarizes the indication and schedule of PCV/PPSV administration to children with high risk conditions according to age group:

SCHEDULE OF PCV 13-PPSV23 VACCINATION SEQUENCE	INDICATION
Age: 24 mos to 5 years •Administer 1 dose of PCV13 if any incomplete schedule of 3 doses of PCV13 was received previously. •Administer 2 doses of PCV13 at least 8 weeks apart if unvaccinated or any incomplete schedule of fewer than 3 doses of PCV13 was received previously. •The minimum interval between doses of PCV13 is 8 weeks. •For children with no history of PPSV23 vaccination, administer PPSV23 at least 8 weeks after the most recent dose of PCV13.	•Chronic heart disease, particularly cyanotic congenital heart disease and cardiac failure •Chronic lung disease, including asthma if treated with high-dose oral corticosteroid therapy •Diabetes mellitus •Cerebrospinal fluid leaks •Cochlear implant(s) •Sickle cell disease and other hemaglobinopathies •Congenital or acquired asplenia, or splenic dysfunction •HIV infection •Chronic renal failure and nephrotic syndrome •Diseases associated with treatment with immunosuppresive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; or solid organ transplantation •Congenital immunodeficiency (includes B- (humoral) or T-lymphocyte deficiency, complement deficiencies (particu larly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease)
Age: 6 yrs to 18 years •Administer 1 dose of PCV13 if they have not previously received this vaccine, regardless of whether the previous vaccine received was PCV7 or PPSV 23 Children aged 2 years to 64 years old, with any 1 of the listed chronic medical conditions should get 1 dose of PPSV23	
NO. OF DOSES OF PPSV 23 ACCORDING TO INDICATION	
Children aged 2 years to 64 years old, with any 1 of the listed chronic medical conditions should get 1 dose of PPSV23	•Chronic heart disease, including heart failure and cardiomyopathies •Chronic lung disease, including chronic obstructive pulmonary disease, emphysema, and asthma •Diabetes mellitus •Cerebrospinal fluid leaks •Cochlear implant(s) •Alcoholism •Chronic liver disease
Children 2 years to 64 years old, with any 1 of the listed immunocompromising conditions should get 2 doses of PPSV23, 5 years apart	Congenital or acquired immunodeficiencies includes B- (humoral) or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease) • HIV infection • Chronic renal failure or nephrotic syndrome • Leukemia or lymphoma • Hodgkin's disease • Generalized malignancy • Iatrogenic immunosuppression (diseases requiring treatment with immunosuppres sive drugs, including long-term systemic corticosteroids and radiation therapy) • Solid organ transplant • Multiple myeloma

Hemophlus influenzae Type b Conjugate Vaccine (Hib)

- Given intramuscularly (IM)
- Indications for children with the following high risk conditions:
  - Chemotherapy recipients, anatomic/functional asplenia including sickle cell disease, HIV infection, immunoglobulin or early component complement deficiency
- Children aged 12-59 months:
  - Unimmunized* or with one Hib vaccine dose received before age 12 months, give 2 additional doses 8 weeks apart
  - With ≥ 2 Hib vaccine doses received before age 12 months, give 1 additional dose
- For children ≤ 5 years old who received a Hib vaccine dose(s) during or within 14 days of starting chemotherapy or radiation treatment, repeat the dose(s) of Hib vaccine at least 3 months after completion of therapy
- For children who are hematopoetic stem cell transplant recipients, revaccination with 3 doses of Hib vaccine given 4 weeks apart, starting 6-12 months after transplant, is recommended regardless of vaccination history.
- Unimmunized* children ≥ 15 months of age and undergoing elective splenectomy should be given 1 dose of Hib-containing vaccine at least 14 days before the procedure
- Unimmunized* children 5-18 years old and with either anatomic or functional asplenia (including sickle cell disease) or HIV infection, should be given 1 dose of Hib vaccine

** Unimmunized children are those without a primary series and booster dose or those without at least one dose of the vaccine after 14 months of age*

Meningococcal Vaccines

- Tetravalent meningococcal (ACYW-135) conjugate vaccine MCV4-D, MCV4-TT, MCV4-CRM given intramuscularly (IM)
- Indicated for those at high risk for invasive disease:
  Persistent complement component deficiencies (including those with inherited or chronic deficiencies in C3, C5-9, properdin, factor D, factor H), anatomic/functional asplenia (including sickle cell disease), HIV, travelers to or resident of areas where meningococcal disease is hyperendemic or epidemic, including countries in the African meningitis belt or the Hajj, or belonging to a defined risk group during a community or institutional meningococcal outbreak

Dosing schedule:

- MCV4-D: minimum age is 9 months. For children 9-23 months give 2 doses 3 months apart. For children 2 years and above give one dose, except in cases of asplenia, HIV and persistent complement component deficiency where 2 doses, 8 weeks apart are recommended.
- MCV4-TT given to children 12 months and above as a single dose
- MCV4-CRM given to children 2 years and above as a single dose
- Revaccinate with a MCV4 vaccine every 5 years as long as the person remains at increased risk of infection
- Co-administration of MCV4 and other vaccines
  MCV4-D and PCV13
  - If MCV4-D is administered to a child with asplenia (including sickle cell disease) or HIV infection, do not administer MCV4-D until age 2 years and at least 4 weeks after the completion of all PCV13 doses
  MCV4-D and Tdap
  - If MCV4-D is to be administered to a child at high risk for meningococcal disease, it is recommended that MCV4-D be given either before or at the same time as DTaP.
  MCV4-TT with Tetanus toxoid (TT) containing vaccines
  - Whenever feasible, MCV4-TT should be co-administered with TT-containing vaccines, or administer MCV4-TT 1 month before the other TT- containing vaccines

Rabies Vaccine

- Given intramuscularly (IM) or intradermally (ID)
- Recommended regimens for pre-exposure prophylaxis:
  - Intramuscular regimen (IM):
    Purified Vero Cell Rabies (PVRV) 0.5 ml OR
    Purified Chick Embryo Cell Vaccine (PCECV) 1 ml given on days 0, 7, 21 or 28
  - Intradermal regimen (ID): PVRV or PCECV 0.1 ml given on days 0, 7, 21 or 28
- A repeat dose should be given if the vaccine is inadvertently given subcutaneously.
- Rabies vaccine should never be given in the gluteal area since absorption is unpredictable.
- In the event of subsequent exposures, those who have completed 3 doses of pre-exposure prophylaxis regardless of the interval between exposure and last dose of the vaccine will require only booster doses given on day 0 and 3. Booster doses may be given IM (0.5 ml PVRV or 1 ml PCECV) or ID (0.1 ml of PVRV or PCECV). There is no need to give rabies immune globulin.

Typhoid Vaccine

- Given intramuscularly (IM)
- Given at a minimum age of 2 years old with revaccination every 2—3 years
- Recommended for travelers to areas where there is a risk for exposure and for outbreak situations as declared by public health authorities

Cholera Vaccine

- Given per orem (PO)
- Given at a minimum age of 12 months as a 2-dose series two weeks apart.
- Recommended for outbreak situations and natural disasters as declared by public health authorities

Hepatitis A Vaccine

- Given intramuscularly (IM)
- Administer 2 doses of Hepatitis A vaccine at least 6 months apart to unvaccinated individuals who are at increased risk for infection:
  - Travelers to or are working in countries with intermediate or high endemicity of infection,
  - Men having sex with men (MSM)
  - Users of injection and non-injection illicit drugs,
  - Working with HAV infected primates or with HAV in research laboratories,
  - With clotting factor disorders and chronic liver disease

Human Papillomavirus Vaccine (HPV)

- Given intramuscularly (IM)
- Give 3 doses of HPV vaccine following the 0, 1-2, and 6 month schedule, regardless of age at vaccine initiation to the following:
  - Children with history of sexual abuse or assault starting at age 9 years
  - Immunocompromised children including those with HIV infection
- HPV vaccination is not recommended during pregnancy. If HPV vaccine is inadvertently given during pregnancy, delay the remaining doses until after pregnancy. Pregnancy testing is not necessary before initiating HPV vaccination.

Dengue Vaccine

Recommendation under review, pending re-labelling of the product

SUMMARY TABLE 2018: Immunization of Pre-Adolescents and Adolescents (7 to 18 yrs.old)

Vaccine	Range of Recommended Age	Dose(s) Needed	Schedule of Immunization	Route of Administration	Precautions & Contradiction
Hep B Vaccine	Unvaccinated 7-18 yrs. old	3	0,1,6 months	IM	• Severe allergic reaction to vaccine component • Moderate to severe illness
Hep A Vaccine	Unvaccinated 7-18 yrs. old	2	2nd dose given at least 6 months from the 1st dose	IM	• Severe allergic reaction to vaccine component • Moderate to severe illness
MMR	Unvaccinated 7-18 yrs. old	2	4 weeks interval between doses	SC	• Severe allergic reaction to vaccine component • Pregnancy • Immunosuppression • Recent receipt of blood products • Moderate to severe illness
	Incompletely vaccinated 7-18 yrs. old	1	2nd dose given anytime but at least 4 weeks from 1st dose		
Varicella	Unvaccinated 7-12 yrs. old	2	Minimum interval between doses is 3 months	SC	• Severe allergic reaction to vaccine component • Pregnancy • Immunosuppression • Recent receipt of blood products • Moderate to severe illness
	Unvaccinated ≥ 13 yrs. old	2	Minimum interval between doses is one month		
	Incompletely vaccinated 7-18 yrs. old	1	Given anytime 7-12 yrs. old at least 3 mos. from the 1st dose,13 yrs.old at least 1 month from the 1st dose		
Influenza Vaccine	9-18 yrs. old	1	Give annually beginning February	IM/SC	• Severe allergic reaction to vaccine component • Moderate to severe illness • History of Guillain-Barre syndrome following a previous dose
Td/Tdap	Unvaccinated 7-18 yrs. old	3	0,1 and 6 months Tdap preferably as the 1st dose then Td for the remaining doses	IM	• Severe allergic reaction to vaccine component, • Moderate to severe illness
	Incompletely vaccinated 7-18 yrs. old	1-2	One dose Tdap then Td for remaining dose		
	Fully vaccinated 7-18 yrs. old (Fully vaccinated defined as 5 doses of DTaP or 4 doses of DTap if the 4th dose was administered on or after the 4th birthday)	1	1 dose Tdap then Td every 10 years		
HPV: Bivalent HPV (2vHPV)	Females: 15-18 yrs. old	3	0,1,6 months	IM	• Severe allergic reaction to vaccine component • Moderate to severe illness • If found to be pregnant after starting immunization, delay remaining doses until completion of pregnancy
Qaudrivalent HPV (4vHPV)/Nonavalent HPV (9vHPV)	Females: 15-18 yrs. old Males: 15-18 yrs.old	3	0,2 and 6 months		
For Females: (2vHPV)/ Quadrivalent HPV (4vHPV/)/ Nonavalent HPV (9vHPV) For Males: 4vHPV/9vHPV	9-14 yrs. old	2	0,6-12 months	IM	• Severe allergic reaction to vaccine component • Moderate to severe illness • If found to be pregnant after starting immunization, delay remaining doses until completion of pregnancy