ORIGINAL ARTICLE

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

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

ABSTRACT

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.

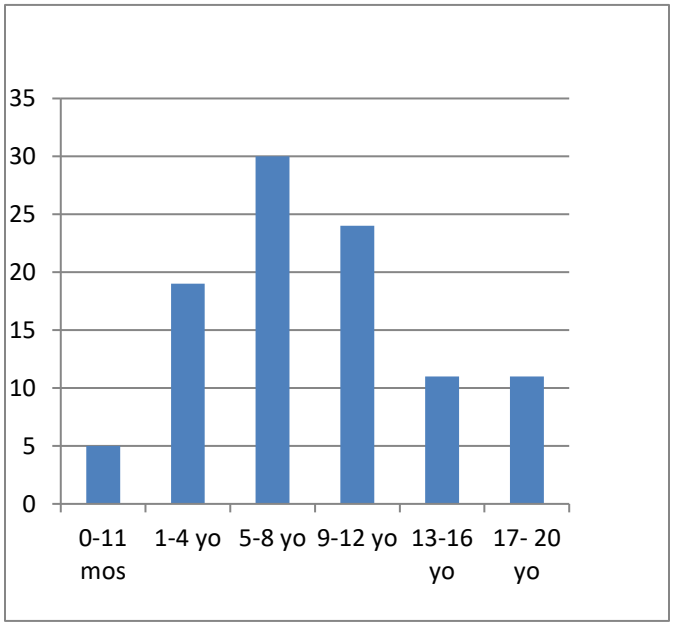

Figure 1. Incidence of Infective Endocarditis by Age Range

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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