INFECTIVE ENDOCARDITIS AT DR GEORGE MUKHARI HOSPITAL: CORRELATING ECHOCARDIOGRAPHY FINDINGS WITH INTRAOPERATIVE FINDINGS

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AUTHOR'S DECLARATION

This study presents original work by the author. It has not been submitted to any other tertiary institution. Where the work of others was used, it has been duly acknowledged in the text.

The research described in this dissertation was carried out in the Department of Clinical Technology, Faculty of Health Sciences, Durban University of Technology under the supervision of Professor JK Adam (Head of the Clinical Technology programme) and the Department of Cardiology, Dr George Mukhari Hospital, Pretoria, South Africa under the supervision of Professor PS Mntla (Head of Department, Cardiology, University of Limpopo).

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DEDICATION

This dissertation is dedicated to:

My family (my mother, Jabulisiwe, my sister, Nontuthuko, my cousin, Hlengiwe), who have honored me by courageously sharing the sorrows and triumphs of our lives. You are truly the inspiration for this work and I thank you for your encouragement, support and patience throughout this study. It meant so much to me during the pursuit of my master's degree and I am grateful for all that you've done for me. To each of you I offer my sincere thanks and deepest gratitude.

The Department of Cardiology, having accepted me as a novice, encouraged me throughout all the years and made it possible for me to study for my master's degree.

ABSTRACT

Introduction

Infective endocarditis is a serious disease that needs rapid diagnosis and accurate risk stratification to offer the best therapeutic strategy. Echocardiography plays a key role in the management of the disease but may be limited in some clinical situations. Moreover, this method is insensitive for very early detection of the infection and assessment of therapeutic response because it does not provide imaging at the molecular and cellular levels. Recently, several novel morphological, molecular and hybrid imaging modalities have been investigated in infective endocarditis and offer new perspectives for better management of the disease.

Aims and objectives of the study

This prospective, quantitative and observational study was investigated at Dr George Mukhari Hospital in Pretoria, South Africa. Infective Endocarditis is a serious disease associated with poor prognosis despite improvements in medical and surgical therapies. Infective Endocarditis results in complex pathogenesis that involves many host-pathogen interactions. Indeed, previous endocardial lesions can lead to the exposure of the underlying extracellular matrix proteins, local inflammation and then thrombus formation, which is termed ‘non-bacterial vegetation’. The project aims to compare the echocardiographic findings (transthoracic echocardiographic-TTE) with intraoperative findings on patients with infective endocarditis. If the correlation existed then the echocardiogram findings were accurate when performed in patients with infective endocarditis.

Methodology

The research participants consisted of forty (40) patients with infective endocarditis at Dr George Mukhari Hospital in Pretoria, South Africa. A cardiologist examined the patient's clinically for features of infective endocarditis. Two techniques were used to assess the infective endocarditis. These included echocardiography and Intraoperative findings (visual and histology). Bloods were cultured to demonstrate the presence of micro-organisms.

Blood was sent to the laboratory for culture in order to detect the presence of micro-organisms. The researcher performed an Echocardiogram to assess which valve was affected, the left ventricular endiastolic diameter (LVED), the left ventricular ensystolic diameter (LVES), the shortening fraction (SF), the ejection fraction (EF) and the size of the vegetation/mass or abscess. For patients requiring a heart surgery, the cardiac surgeon performed the valve replacement, and the intra-operative findings was assessed visually to confirm the presence of vegetation or abscess and leaflets destruction. During the operation, which was performed by the same cardiac surgeon, a biopsy sample was taken for histological examination to confirm the presence of vegetation or abscess. Thereafter, the cardiac surgeon performed the valve repair/ replacement/ bioprosthesis. The researcher was blinded to the findings in the theatre as the researcher was not present in the theatre. The results from the laboratory was sent to the researcher. The researcher was then able to confirm the presence of vegetation or mass/ abscess and leaf destruction.

Results

The histology confirmed what was seen on echocardiographical findings and intraoperative findings (visual). The intraoperative and echocardiography findings showed thirty two of 40 (80%) vegetation, two of 40 (5%) perforation, four of 40 (10%) pseudoaneursym and two of 40 (5%) abscesses. The prognosis of patients with poor ejection fraction (40-50% EF) was poorer than those with good ejection

fraction (60-75%). The clinical findings of all patients confirmed infective endocarditis and thirty two of 40 (80%) blood cultures were positive and eight of 40 (20%) were negative. There were seven of 40 (17,5%) patients who showed poor correlation 40-50% between echocardiographical findings and post-operative findings. The results of thirty three of 40 (82%) patients showed moderate correlation 69% between the echocardiographical findings and post-operative findings.

Conclusion

My findings of the study was that eight of 40 (20%) had stenosis and thirty two of 40 (80%) had regurgitation in patients who had infective endocarditis. There was an overall moderate association (r=0.68) between echocardiography and the intraoperative findings in all patients for LVES.

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To participants, thank you for participating in this study and sharing your medical knowledge. It is hoped that your participation in this study will contribute to providing a better analysis of diagnosis and appropriate medical/surgical management of other patients.

To Dr P Shembe, Director: Clinical Service of Dr George Mukhari Hospital, thank you for granting me permission to access cardiac patients.

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LIST OF ABBREVIATIONS

ABE - Acute bacterial endocarditis

AO – Aorta

AV - Aortic valve

AMV - Aortic mitral valve

Avv - Aortic valve vegetation

CD4 - Cluster Difference 4

CHF - Congestive Heart Failure

CoNS - Coagulase-negative staphylococci

CPD - Continued professional development

CT - Computed tomography

CTA - Computed tomography angiography

DGMH - Dr George Mukhari Hospital

DOH - Department of Health

DUT - Durban University of Technology

ECG - Electrocardiogram

ECMA - Extracranial mycotic aneurysm

EF - Ejection fraction

GP - Gauteng Province

HIV - Human immunodeficiency virus

HPCSA - Health Professions Council of South Africa

ICMA - Intracranial mycotic aneurysm

IE - Infective endocarditis

IV - Intravenous dug

IVDU - Intravenous drug user

IREC - Institutional Research Ethics Committee

LA - Left atrium

Lax - Long axis

LV - Left ventricle

LVED - Left ventricular endiastolic diameter

LVES - Left ventricular ensystolic diameter

MAs - Mycotic aneurysm

MRA - Magnetic resonance angiography

MRI - Magnetic resonance imaging

MV - Mitral valve

Mvv - Mitral valve vegetation

PCR - Polymerase chain reaction

PMV - Posterior mitral valve

PVE - Prosthetic valvular endocarditis

RA - Right atrium

RV - Right ventricle

SANAS - South African National Accreditation System

Sax - Short axis

SF - Shortening fraction

TEE - Trans esophageal echocardiographic

TTE - Trans thoracic echocardiographic

TV - Tricuspid valve

VEG - Vegetation

Vs - Versus

CHAPTER ONE: INTRODUCTION

Infective endocarditis (IE) is an infection of the endocardial surface of the heart, which may include one or more heart valves, the mural endocardium, or a septal defect. It causes fever, heart murmurs, petechiae, anaemia, embolic phenomena and endocardial vegetations. Vegetations may result in valvular incompetence or obstruction and myocardial abscess. Diagnosis requires demonstration of micro-organisms on blood culture and usually vegetations on echocardiography. Treatment consists of prolonged antimicrobial therapy and sometimes surgery. Endocarditis can occur at any age. Males are affected about twice as often as females. Intravenous (IV) drug abusers and immune-compromised patients are at high risk (Sexton and Mick, 2000). The normal heart is relatively resistant to infection. Fungi and bacteria may not easily adhere to the endocardial surface and blood flow helps prevent them from settling on the endocardial structures. Two factors are generally required for endocarditis: a predisposing abnormality of the endocardium and micro-organisms on normal valves.

Endocardial factors: Endocarditis usually involves the heart valves. Major predisposing factors are congenital heart defects, rheumatic valvular disease, bicuspid or calcific aortic valves, mitral valve prolapse and hypertrophic cardiomyopathy. Prosthetic valves are at particular risk (Wilson et al., 2007). Occasionally mural thrombi, ventricular septal defects and patent ductus arteriosus sites become infected. The actual nidus for infection is usually sterile fibrin platelet vegetation formed when damaged endothelial cells release tissue factor (Wilson et al., 2007).

Infective Endocarditis occurs most often on the left side of the heart (i.e. mitral or aortic valve) (Durack et al., 1994). About 10-20% of cases are right-sided (tricuspid or pulmonic valve). Intravenous drug abusers have a much higher incidence of right-sided endocarditis (about 30-70%).

Micro-organisms: Micro-organisms that infect the endocardium may originate from distant infected sites (e.g. cutaneous abscesses, inflamed or infected gums, urinary tract infection) or obvious portals of entry, such as a central venous catheter or a drug injection site. Almost any implanted foreign material (e.g. ventricular or peritoneal shunt, prosthetic device) is at risk of bacterial colonisation, thus becoming a source of bacteraemia and hence endocarditis. Endocarditis also may result from asymptomatic bacteraemia, which typically occurs during invasive dental, medical or surgical procedures. Even tooth-brushing and chewing can cause bacteraemia (usually due to *Streptococci virdans)* in patients with gingivitis (Durack et al., 1994).

Causative micro-organisms vary by site of infection, source of bacteraemia and host risk factors (e.g. IV drug abuse) but overall *Streptococci* and *Staphylococcus aureus (S aureus)* cause 80-90% of cases. *Enterococci*, Gram-negative bacilli, HACEK organisms (haemophilus species, *Aggregatibacter* [formerly *Actinobacillus*]*, action mycetomes, Cardio bacterium hominis, Eikenella corrodens* and *Kingella kingae)* and fungi cause most of the rest (i.e., 10%). The ability of *Staphylococcus aureus* to adhere to fibronectin may play a role, as may dextran production by *Streptococci virdans*. After colonisation vegetation, micro-organisms are covered by a layer of fibrin and platelets, which prevents access by neutrophils and complements and thus blocks host defences (Mathew et al., 1995).

The Duke criteria were used for diagnosis of IE (Li et al., 2000). They are based on the following major and minor criteria:

Major criteria

1. Positive blood cultures for IE.

A. Typical micro-organisms consistent with IE from two separate blood cultures, as noted below:

- *Streptococci viridans, Streptococcus bovis, Staphylococcus aureus*; or

- Community acquired enterococci, in the absence of a primary focus;

or

B. Micro-organisms consistent with IE from persistently positive blood cultures defined as:

- two or more positive cultures of blood samples drawn >12 hours apart

- all of three or a majority of four or more separate cultures of blood (with first and last sample drawn >1 hour apart)

2. Evidence of endocardial involvement

A. Echocardiogram positive for IE

Vegetation

Abscess

New partial dehiscence of prosthetic valve

B. New valvular regurgitation (worsening or changing of pre-existing murmur is not sufficient)

Minor criteria:

Predisposition: predisposing heart condition, injection drug use

Fever: temperature >38^0C

Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhages, Janeway's lesions

Immunologic phenomena: glomerulonephritis, Olser's nodes, Roth's spots, rheumatoid factor positive

Microbiological evidence: positive blood culture but does not meet a major criterion (Sexton et al., 2000).

In the present study transthoracic echocardiography (TTE) rather than trans-oesophageal echocardiography (TEE) was performed. Although TEE is somewhat

more accurate (i.e., capable of revealing vegetations too small to be seen on TTE), it is invasive and more costly.

The project aims to compare the echocardiographic findings (TTE) with intra-operative findings on patients with IE.

Objectives

1. To compare the echocardiographic findings with intraoperative and histological findings.

2. To assess the outcomes of the patients with IE at Dr George Mukhari Hospital (DGMH).

3. To assess the severity of complications in patients with IE at DGMH.

4. To compare blood cultures of positive IE to echocardiographic findings.

5. To assess the effect of IE on left ventricular function.

CHAPTER TWO: STUDY BACKGROUND AND LITERATURE REVIEW

2.1 STUDY BACKGROUND

2.1.1 INTRODUCTION

Infective Endocarditis is a serious disease associated with poor prognosis despite improvements in medical and surgical therapies. Infective Endocarditis results in complex pathogenesis that involves many host-pathogen interactions. Indeed, previous endocardial lesions can lead to the exposure of the underlying extracellular matrix proteins, local inflammation and then thrombus formation, which is termed 'non-bacterial vegetation' (Habib et al., 2009). In the case of bacteraemia, valves with pre-existing sterile vegetations or tissues with minimal lesions can be colonised because of strong interactions between the bacteria, platelets and endothelial cells via several bacterial surface proteins or plasma-bridging molecules (Habib et al., 2009).

This process leads to the recruitment of circulating inflammatory cells and the release of cytokines and procoagulant factors, which contribute to the enlargement of vegetations and the protection of bacterial pathogens from host defences (Thuny et al., 2011). Ultimately, valvular and perivalvular tissues are destroyed, thus increasing the risk of valve dysfunction, abscess formation and embolisation (Thuny et al., 2011).

Moreover, in addition to embolic events, other extracardiac life-threatening complications may occur, such as infectious aneurysms and intracranial and visceral haemorrhages. Therefore, early and reliable diagnostic and risk stratification strategies are critical to reduce delays to the start of appropriate antimicrobial therapy and to identify patients who require urgent valve surgery (Baddour et al., 2005). As described in recent international recommendations, echocardiography is a simple and accurate method for detecting endocardial damage in IE and helping in risk stratification (Baddour et al., 2005).

However, echocardiography studies may be limited in some clinical situations and this technique is insensitive to very early detection of infection because it does not provide an imaging assessment of IE at the molecular and cellular levels (Baddour et al., 2005). Recently, other morphological and molecular imaging strategies have emerged for the detection of endocardial involvement and extracardiac complications (Evangelista et al., 2004). The aims of this review is to provide an update on the value of echocardiography in the management of IE, to discuss the potential role of other imaging techniques and, finally, to consider the challenges and perspectives in the imaging investigations (Evangelista et al., 2004).

2.1.2 MORPHOLOGICAL IMAGING OF ENDOCARDIAL DAMAGE AND ITS CONSEQUENCES

2.1.2.1 Echocardiography: The main imaging modality

Echocardiography plays a key role not only in the diagnosis of IE but also in the prognostic assessment and follow-up under therapy and during surgery (Habib et al., 2010). Recently, recommendations for the practice of echocardiography in IE have been published, to provide an update on the value and limitations of this technique in IE and to define the optimal use of TTE and TEE (Habib et al., 2010).

2.1.2.2 Echocardiography for the diagnosis of infective endocarditis

Although IE may present with several very different initial symptoms, its diagnosis usually relies on the association of clinical, microbiological and morphological criteria, which are included in the modified Duke classification (Li et al., 2000). By detecting several forms of endocardial damage, echocardiography remains an accurate method for providing the major diagnostic criteria of IE (Li et al., 2000). Knowledge of the anatomical features of IE is fundamental in order to understand, analyse and describe the echocardiographic findings better (Table 1) (Habib et al., 2010).

Table 1: Anatomical and echocardiographic definitions (Liu et al., 2009).

	Surgery/necropsy	Echocardiography
Vegetation	Infected mass attached to an endocardial structure or on implanted intracardiac material	Oscillating or non-oscillating intracardiac mass on valve or other endocardial structures, or on implanted intracardiac material
Abscess	Perivalvular cavity with necrosis and purulent material not communicating with the cardiovascular lumen	Thickened, non-homogeneous perivalvular area with echodense or echolucent appearance
Pseudo-aneurysm	Perivalvular cavity communicating with the cardiovascular lumen	Pulsatile perivalvular echo-free space, with colour Doppler flow detected
Perforation	Interruption of endocardial tissue continuity	Interruption of endocardial tissue continuity traversed by colour Doppler flow
Fistula	Communication between two neighbouring cavities through a perforation	Colour Doppler communication between two neighbouring cavities through a perforation
Valve aneurysm	Saccular outpouching of valvular tissue	Saccular bulging of valvular tissue
Dehiscence of a prosthetic valve	Dehiscence of the prosthesis	Paravalvular regurgitation identified by TTE/TEE, with or without rocking motion of the prosthesis

Trans esophageal Echocardiographic (TEE) is the initial technique of choice for investigation (Li et al., 2000). A normal scan in low-risk patients provides rapid non-invasive confirmation that the diagnosis is unlikely (Liu et al., 2009). Moreover, TTE is better than TEE for the detection of anterior cardiac abscesses and for haemodynamic assessment of valvular dysfunction (Liu et al., 2009).

Because of its higher sensitivity and specificity, TEE is recommended in cases of negative TTE associated with high clinical suspicion, poor TTE quality, presence of prosthetic valves or an intracardiac device, and positive TTE (Liu et al., 2009). In preliminary studies, three-dimensional TEE provided incremental value over two-dimensional TEE in its ability to identify and localise vegetations accurately and to identify complications such as abscesses, perforations and ruptured chordate (Liu et al., 2009). Thus, echocardiography must be done rapidly and repeated once a week as soon as it is negative but the condition is suspected (Liu et al., 2009).

Valve surgery should be performed in an urgent setting when a large vegetation (> 10 mm) is present following one or more embolic episodes (Thuny et al., 2010). In addition, when associated with other known predictors of a complicated course (heart failure, persistent infection under therapy, abscess and prosthetic endocarditis), the presence of a large vegetation (> 10 mm) indicates an earlier surgical decision (Thuny et al., 2010). Finally, the decision to operate in the case of an isolated very large vegetation (> 15 mm) is more difficult and must be specific for the individual patient (Thuny et al., 2010).

Surgery may be preferred when a valve repair seems possible, particularly in mitral valve IE. Nevertheless, the prediction of embolism remains challenging and should take into account other criteria, such as the type of micro-organisms (*Staphylococcus aureus*) and conditions associated with a prothrombogenic state (atrial fibrillation, diabetes, etc.). Recently, a randomised trial demonstrated that early surgery in patients with large vegetations and significant valve dysfunction significantly reduced the composite endpoint of death from any cause and embolic events by effectively decreasing the risk of systemic embolism compared with conventional therapy (Kang et al., 2012).

Although this result is of crucial importance, it was limited by the fact that it was obtained in a population with a very low operative risk. Thus, there is now strong evidence that early surgery reduces embolic risk but there is a need for better risk stratification in order to evaluate accurately the benefit-risk ratio of this procedure (Kang et al., 2012). Indeed, for high embolic risk associated with low or intermediate

predicted operative mortality (computed by scoring systems), the benefit of early surgery would be greater (Thuny et al., 2010).

Endocarditis has local and systemic consequences:

Local consequences: Severe valvular regurgitation may develop suddenly, causing heart failure and death, usually due to mitral or aortic valve lesions. Local consequences include formation of myocardial abscesses with tissue destruction and sometimes conduction system abnormalities. Aortitis may result from continuous spread of infection (Weiss and Goldblum, 2001). Prosthetic valve infections are particularly likely to cause valve ring abscesses, obstructing vegetations, myocardial abscesses and mycotic aneurysms manifesting as valve obstruction, conduction disturbances and strokes/infarcts (Weiss and Goldblum, 2001)

Systemic consequences: Right-sided lesions typically produce septic pulmonary emboli, which may result in pulmonary infarction, pneumonia or emphysema. Systemic consequences are primarily due to embolisation of infected material from the heart valve and primarily in chronic infection (Saunders, 2005). Left-sided lesions may embolise to any tissue, particularly the kidneys and spleen. Mesentry mycotic aneurysms can form in any major artery (Saunders, 2005). Diffuse glomerulonephritis may result from immune complex deposition. Cutaneous and retinal emboli are common (Saunders, 2005).

Infective Endocarditis may have a subacute course or a more acute, fulminant course with greater potential for rapid decompensation (Braunwald,1996). Subacute bacterial endocarditis, although aggressive, usually develops insidiously and progresses slowly. Often no source of infection or portal of entry is evident (Sternberg, 2004).

Subacute bacterial endocarditis is caused most commonly by *Streptococci* (especially *viridans*), micro-aerophillic, anaerobic and nonenterococcal group D *Streptococci* and *Enterococci* and less commonly by *Staphylococcus aureus, Staphylococcus epidermidis, Gemella morbillorum, Abiotrophia defective, Granulicatella sp* and fastidious *Haemophilus sp (*Saunders, 2005). Subacute bacterial endocarditis often

develops on abnormal valves after asymptomatic bacteraemia due to periodontal procedures (Saunders, 2005).

Acute bacterial endocarditis (ABE) usually develops abruptly and progresses rapidly (Sternberg, 2004). A source of infection or portal of entry is often evident. When bacteria are virulent or bacterial exposure is massive, ABE can affect normal valves. It is usually caused *by S. aureus, group A haemolytic Streptococci, Pneumococci* or *Gonococci* (Sternberg, 2004).

Prosthetic valvular endocarditis (PVE) develops in 2-3% of patients within one year after valve replacement and in 0.5%/year thereafter (Sternberg, 2004). It is more common after aortic than after mitral valve replacement and affects mechanical and bioprosthetic valves equally. Early onset infections are caused mainly by contamination during surgery with antimicrobial resistant bacteria (Braunwald, 1996). Late onset infection is caused mainly by contamination with low virulence organisms during surgery or by transient asymptomatic *bacteraemias*, most often with *Streptococci* and the fastidious Gram-negative bacilli*, Haemophilus sp., Actinobacillus, Actinomycete comitans and Cardiobacterium horminis* (Braunwald,1996).

Timing of surgery requires experienced clinical judgement (Reynolds et al., 2003). Surgery is frequently required for abscess formation or persistent infection despite proper antimicrobial therapy or severe valvular regurgitation and intractable heart failure (Bayer et al., 1998). If heart failure caused by a correctable lesion is worsening, surgery may be required after only 24 to 72 hours of antimicrobial therapy (Fuster and Walsh, 2009). In patients with prosthetic valves, surgery may be required when TEE shows valve dehiscence or a paravalvular abcess, when valve dysfunction precipitates heart failure, when recurrent emboli are detected or when the infection is caused by an antimicrobial-resistant organism (Fuster and Walsh, 2009).

Untreated IE is always fatal. The prognosis is also poorer for people with aortic or multiple valve involvement, large vegetations, polymicrobial bacteraemia, prosthetic valve infections, mycotic aneurysms, valve ring abscesses and major embolic events (Andrews et al., 2001). Even with treatment, death is more likely and the prognosis is generally poorer for older people who have infection with resistant organisms, an underlying disorder, or a long delay in treatment (Andrews et al., 2001).

The mortality rate for *Streptococcal viridians* endocarditis without major complications is <10% but it is virtually 100% for *Aspergillus* endocarditis after prosthetic valve surgery (Andrews et al., 2001). The prognosis is better with right-sided endocarditis than left-sided endocarditis because tricuspid valve dysfunction is tolerated better, systemic emboli are absent and right-sided *Staphlococcus aureus* endocarditis responds better to antimicrobial therapy (Andrews et al., 2001).

A positive valve culture or histology is defined as definite endocarditis. Further refinements in the diagnosis have occurred with the use of echocardiography. Transoesophageal echocardiography is preferred over the transthoracic approach because it usually provides superior imaging for detecting vegetation and absesses (Andrews et al., 2001). Major criteria for probable endocarditis are persistent bacteraemia with a new regurgitant heart murmur or valvular heart disease with vasculitis or negative or intermittent bacteraemia with fever and a new regurgitant heart murmur with vasculitis (Andrews et al., 2001).

These criteria include subconjunctival and soft palate petechiae, haemorrhages within the nail beds (splinter haemorrhages), painful subcutaneous nodules on the palms or soles (Osler's nodes) and generalised rashes (Andrews et al., 2001). A careful physical examination may disclose skin or mucosal lesions in about 50% cases (Brusch, 2007). Patients may also present with painful embolic lesions on fingers or toes, which may be visible (Andrews et al., 2001).

Almost always, a regurgitant heart murmur is heard, usually in the mitral or aortic valve position (Baddour et al., 2005). New or changing murmurs in patients with pre-existing murmurs are noted in about 30% of cases. A widening of the pulse pressure may be a sign of aortic valve dehiscence, an indication for urgent surgical intervention. Similarly, bradycardia progressing to heart block can be caused by a septal abcess, which also requires open surgical debridement and drainage (Andrews et al., 2001).

Splenomegaly, reported in about 20% of cases, is more likely in patients who have been ill for months rather than days or weeks (Andrews et al., 2001). Streptococci, especially *Streptococcus viridans*, have historically been responsible for a large percentage of cases of native valve endocarditis. However, in more recent series, *S.aureus* may be as common or even more common. Certain *Streptococci viridans*, such as *Streptococcus mitis*, may be nutritionally variant and require active vitamin B6 (Baddour et al., 2005). Such variants account for 10% of cases, and tend to be less susceptible to penicillin. Enterococci are responsible for up to 10% cases; some strains may be resistant to not only penicillin, but also to vancomycin and aminoglycosides (Baddour et al., 2005).

The microscopic appearance of ABE differs markedly from that of subacute disease (Brusch, 2007). Vegetation that contains no fibroblasts develops rapidly, with no evidence of repair (Brusch, 2007). Large amounts of both polymorph nuclear leukocytes and organisms are present in an ever-expanding area of necrosis. This process rapidly produces spontaneous rupture of leaflets, of the papillary muscles and of the chordae tendinae (Brusch, 2007). The complications of ABE result from intracardiac disease and metastatic infection produced by suppurative emboli (Brusch, 2007). Because of their shortened course, immunological phenomena are not part of acute IE (Brusch, 2007).

Since the 1960's the clinical characteristics of IE have changed significantly (Cabell et al., 2003). The dramatic graying of the disease and the increase in recreational drug use and proliferation of invasive vascular procedures underline this phenomenon

(Cabell et al., 2003). Varieties of IE that were uncommon in the early antibiotic era have become more prominent (Rice et al., 1991). Cases of IE have markedly increased (Geraci, 1958). Valvular infections have entered the era of IE, caused by intravascular devices and procedures (Brusch, 2007).

Underlying valvular pathology has also changed (Brusch, 2007). Rheumatic heart disease currently accounts for less than 20% of cases, and 6% of patients with rheumatic heart disease eventually develop IE (Brusch, 2007). Approximately 50% of elderly patients have calcified aortic stenosis as the underlying pathology (Brusch, 2007). Congenital heart disease accounts for 15% of cases, with the bicuspid aortic valve being the most common example (Brusch, 2007).

Other contributing congenital abnormalities include ventricular septal defects, patent ductus arteriosus and tetralogy of Fallot (Brusch, 2007). Atrial septal defect (secundum variety) is rarely associated with IE (Brusch, 2007). Mitral valve prolapse is the most common predisposing condition found in young adults and is the predisposing condition in 30% of cases (Brusch, 2007). Infective Endocarditis complicates 5% of cases of asymmetrical septal hypertrophy, the mitral valve (Brusch, 2007).

The most significant risk factors for IE are residual valvular damage caused by a previous attack of endocarditis. Many possible risk factors for the development of pacemaker IE have been described, including diabetes mellitus, age and use of anticoagulants and corticosteroids. The evidence of these is conflicting. The main risk factor is probably surgical intervention in any part of the pacemaker system, especially elective battery replacements. Other significant risk factors for pacemaker IE include the development of a postoperative haematoma, inexperience of the surgeon, and a preceding temporary transvenous pacing (Brusch, 2007).

2.1.3 ECHOCARDIOGRAPHY

Echocardiography is central to the diagnosis and management of patients with IE (Reynolds et al., 2003). Echocardiograhic evidence of an oscillating intracardiac mass or vegetation, an annular abscess, prosthetic valve partial dehiscence and new valvular regurgitation are major criteria in the diagnosis of IE (Reynolds et al., 2003).

Echocardiography should be performed in all cases of suspected IE (Reynolds et al., 2003). Whether TTE or TEE should be performed first depends on the clinical scenario (Reynolds et al., 2003). If the clinical suspicion is relatively low or imaging is likely to be of good quality, then it is reasonable to perform TTE. When imaging is difficult or poor, TEE should be considered. If any circumstances preclude securing optimal echocardiographic windows, including chronic obstructive lung disease, previous thoracic surgery, morbid obesity, or other conditions, then TEE should be performed instead of TTE (Reynolds et al., 2003).

If TTE is negative and clinical suspicion remains low, then other clinical entities should be considered (Bayer et al.,1998). If TEE shows vegetation but the likelihood of complications is low, then subsequent TEE is unlikely to alter initial medical management. On the other hand, if clinical suspicion of IE or its complications is high (e.g in prosthetic valve, staphylococcal bacteraemia or new atrioventricular block), then negative TTE will not definitely rule out IE or its potential complications and TEE should be performed first (Reynolds et al., 2003).

Investigation in adults have shown TEE to be more sensitive than TTE for detection of vegetation and abscesses (Reynolds et al., 2003). In addition, in the setting of a prosthetic valve, transthoracic images are greatly hampered by the structural components of the prosthesis and are inadequate for assessment of the perivalvar area where those infections often start (Reynolds et al., 2000). Although cost-effectiveness calculations suggest that TEE should be the first examination in adults

suspected of having IE, particularly in the setting of staphylococcal bacteraemia, many patients are not candidates for immediate TEE because of oral intake during the preceding six hours or because the patients are in institutions that cannot provide 24-hour TEE services (Reynolds et al., 2003).

Both TEE and TTE may produce false negative results if vegetations are small or have already embolised (Bayer, 1993). Even TEE may initially miss a perivalvular abscess, particularly when the study is performed early in the patient's illness (Daniel et al., 1991). In such cases, the incipient abscess may be seen only as nonspecific perivalvular thickening, which on repeat imaging across several days may become recognisable as it expands and forms cavities. Similarly, perivalvular fistulae and pseudo-aneurysms develop over time and negative early TEE images do not exclude the potential for their development (Bayer et al., 1998).

False positive results from TEE or TTE studies may occur when valvular abnormalities are seen that may be due to a current infection. One approach to minimising confusion from these structures is to exploit the high frame rates that are often available with current equipment to improve temporal resolution and clearly visualise rapidly moving structures such as micro cavitations from prosthetic valves or fibrillar components (Erbel et al., 1988).

Several echocardiographic features identify patients at high risk of a complicated course or with a need for surgery. These features include large vegetations, severe valvular insufficiency, abscess cavities or pseudoaneurysms, valvular perforation or dehiscence, and evidence of decompensated heart failure (Erbel et al., 1988). The ability of echocardiographic features to predict embolic events is limited. The greatest risk appears to occur with large vegetations (>10 mm in diameter) on the anterior mitral leaflet. Vegetation size and mobility must be taken into account along with bacteriologic factors and other indications for surgery, when considering early surgery to avoid embolisation (Erbel et al., 1988).

2.1.4 INFECTIVE ENDOCARDITIS ON VALVES

2.1.4.1. Mitral valve

The ability of M-mode and two-dimensional echocardiography to visualise vegetations on the valves affected by endocarditis is one of the major applications of echocardiography. The echocardiographic criterion for the diagnosis of a vegetation is the finding of an echogenic mass on one of the valve leaflets. Figure 1 shows one of the original M-mode echocardiograms with a vegetation on a posterior mitral leaflet. The echocardiographic diagnosis consists of a mass of somewhat “shaggy” echoes on the valve leaflets (Dillon, 1973).

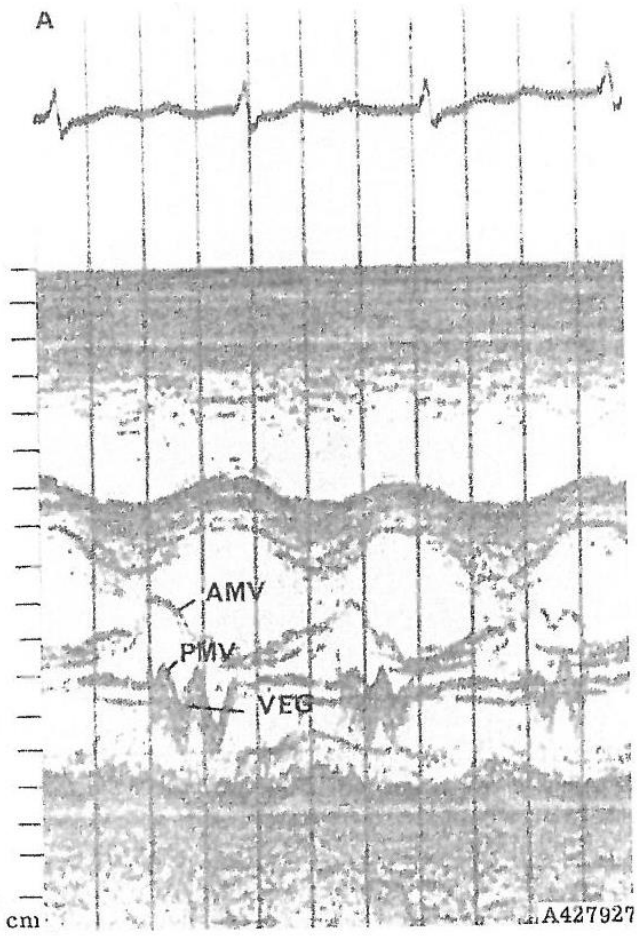


Figure 1: One of the original M-mode echocardiograms with a vegetation on posterior mitral leaflets (Dillon, 1973).

2.1.4.2 Aortic valve

Vegetations on the aortic valve are similar to those on the mitral valve. The diagnosis of aortic valve vegetations is easier because multiple echoes from the aortic valve are not as common as they are in the non-infected mitral valve. Figure 2 is an early tracing from a patient with aortic valve vegetation. Again, one sees increased echoes from the aortic valve leaflets with no restriction of motion. The echoes from the vegetation may be seen best either in systole or in diastole, depending on the direction of the ultrasonic beam. A mobile vegetation is more apparent on the M-mode echocardiogram.

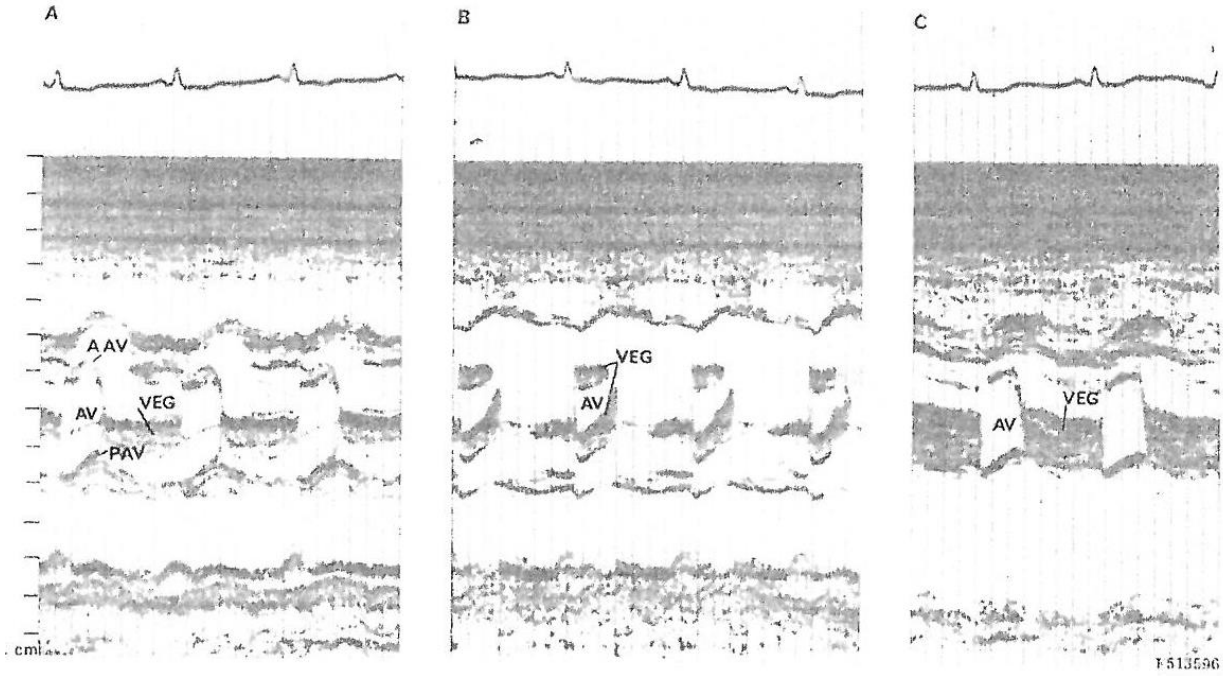


Figure 2: Aortic valve echocardiograms of a patient with bacterial endocarditis and vegetation (VEG) on the aortic valve (AV), AAV=anterior aortic valve leaflet; PAV=posterior aortic valve leaflet (Dillon, 1973).

Figure 3 demonstrates a vegetation on the aortic valve that is recorded as a mass of echoes within the aorta in diastole. In addition, part of the vegetation can be seen in the left ventricular outflow tract above the mitral valve. Recording these abnormal echoes within the left ventricular outflow tract is more convincing than merely finding excess echoes on the aortic valve.

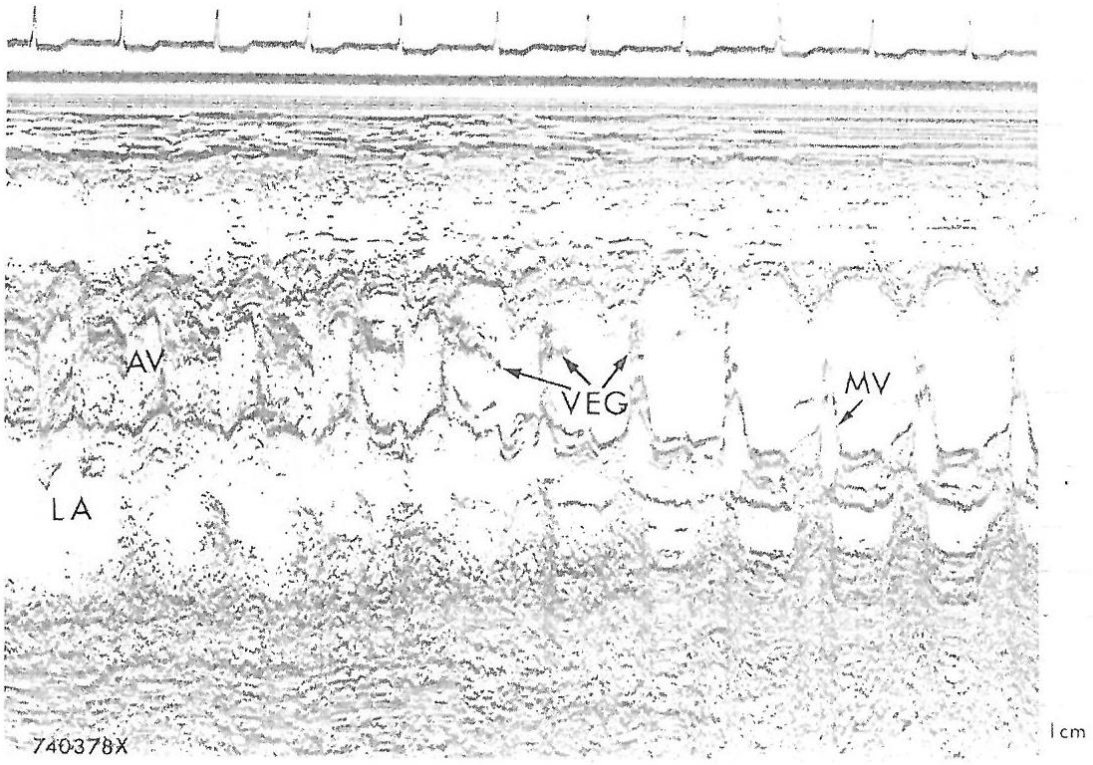


Figure 3: M-mode scan of a patient with bacterial endocarditis and vegetation on the aortic valve (AV). During diastole echoes from the vegetations (VEG) extend into the left ventricular outflow tract above the mitral valve (MV). LA=left atrium (Dillon,1973).

One report described vegetation that produced lethal obstruction to blood flow into the aorta. Vegetations large enough to obstruct the mitral valve have also been detected echocardiographically (Dillon, 1973).

2.1.4.3 Tricuspid valve

Vegetations involving the tricuspid valve have been noted on the M-mode echocardiogram. Their appearance is similar to those seen on the mitral valve. Occasionally, one might note an unusually large vegetation such as the one in Figure 4 involving the tricuspid valve. In this case, the mass is so large that it is difficult to distinguish from a neoplasm. It must be emphasised that finding a mass on a valve is not specific for a vegetation.

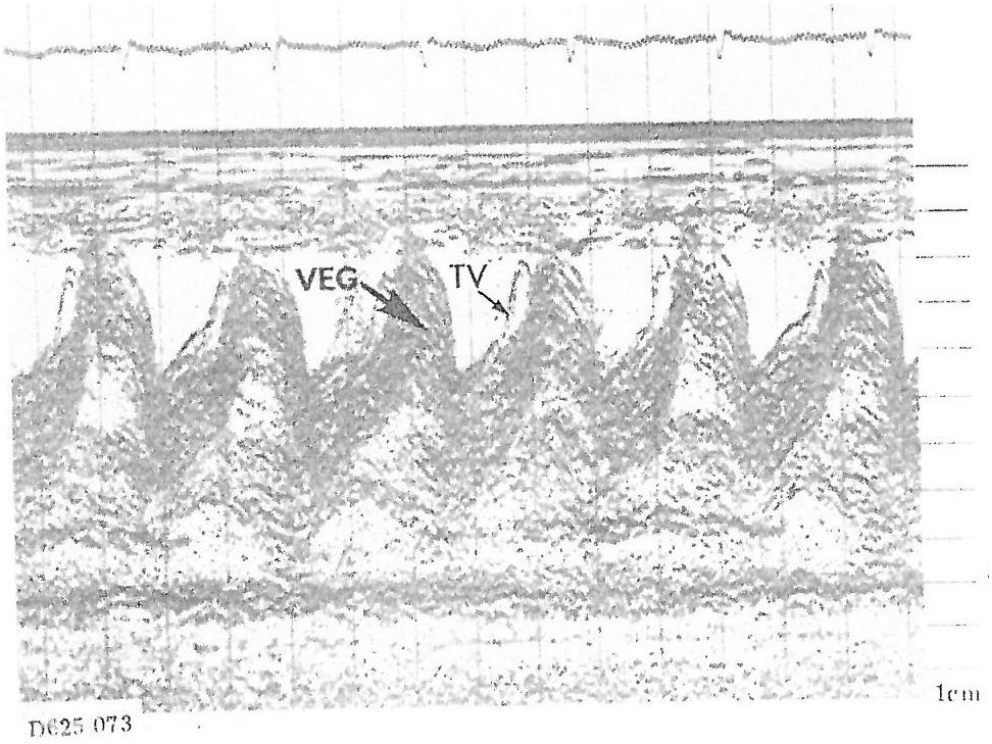


Figure 4: M-mode echocardiogram demonstrating a massive bacterial vegetation (VEG) on the tricuspid valve (TV) (Covarrubias et al., 1977).

In Figure 5, the tricuspid valve shows an echo-producing mass near the posterior tricuspid valve leaflet. These “shaggy” echoes actually originated from a clot that was trapped in the tricuspid valve. No evidence of a vegetation was found (Cabell et al., 2003).

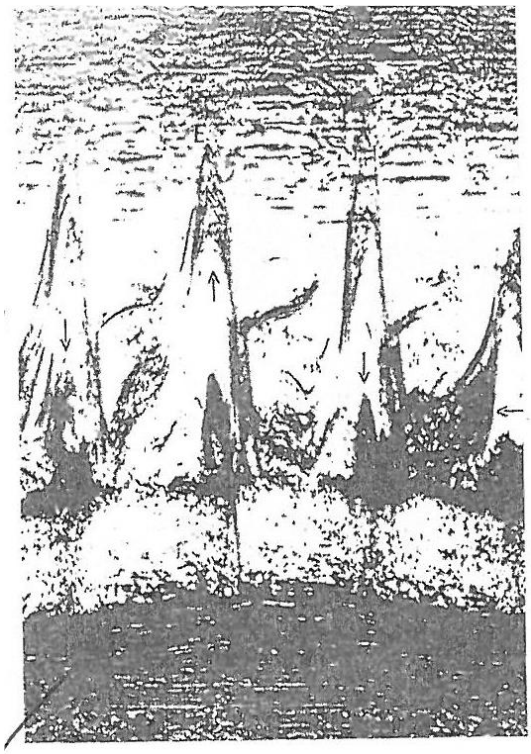


Figure 5: Tricuspid valve echocardiogram showing multiple “shaggy” echoes (arrows) attached to the tricuspid valve (TV). These echoes originated from a clot that was trapped within the tricuspid valve and simulated a vegetation (Cabell et al., 2003).

2.1.5 TWO –DIMENSIONAL ECHOCARDIOGRAPHY ON VALVES

Two-dimensional echocardiography is the preferred technique for detecting vegetations. The partially oriented examination provides a better assessment of size and motion of the abnormal masses (Mugge et al., 1989).

Figure 6 demonstrates mobile vegetation on the mitral valve. This mobile mass of tissue (*arrow)*, attached to a flail mitral valve, can be seen protruding into the left atrium in systole and into the left ventricular outflow tract in diastole. The real-time examination was striking as this mass flopped about within the heart.

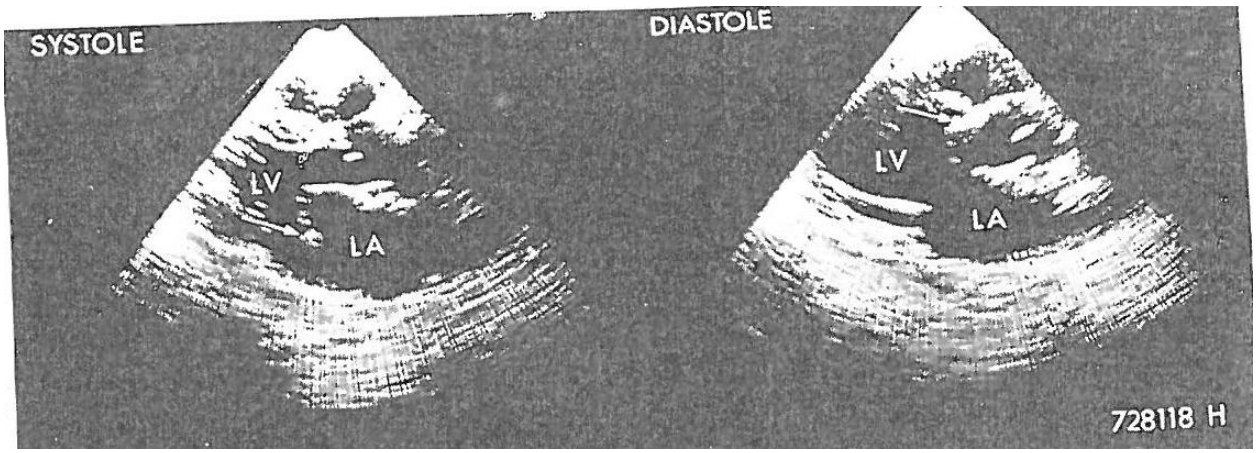


Figure 6: Long-axis echocardiogram demonstrating a mobile vegetation on the anterior mitral leaflet. In systole, the vegetation protrudes into the left atrium. In diastole, the vegetation moves into the left ventricular outflow tract. LV=left ventricle; LA=left atrium (Mugge et al., 1989).

Figure 7 demonstrates vegetation on both mitral valve leaflets.

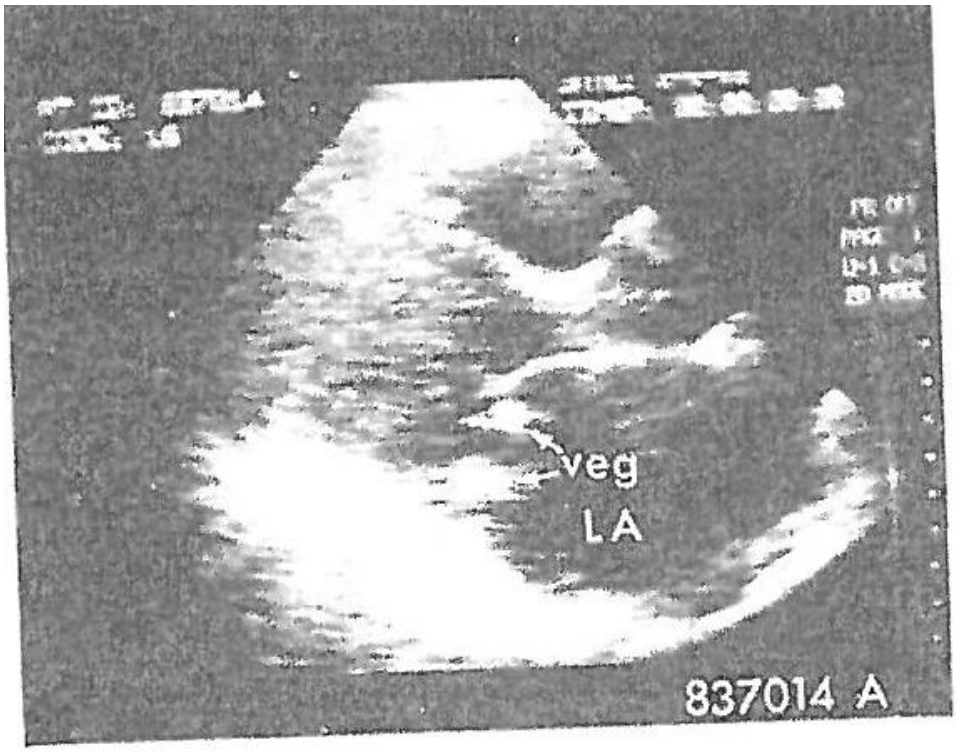


Figure 7: Long-axis two-dimensional echocardiogram of a patient with vegetations on both mitral leaflets. LA=left atrium (Covarrubias et al., 1977).

The patient illustrated in Figure 8 had endocarditis involving the aortic valve. The vegetation (veg) can be seen protruding into the left ventricular outflow tract in both the long-axis and short-axis views.

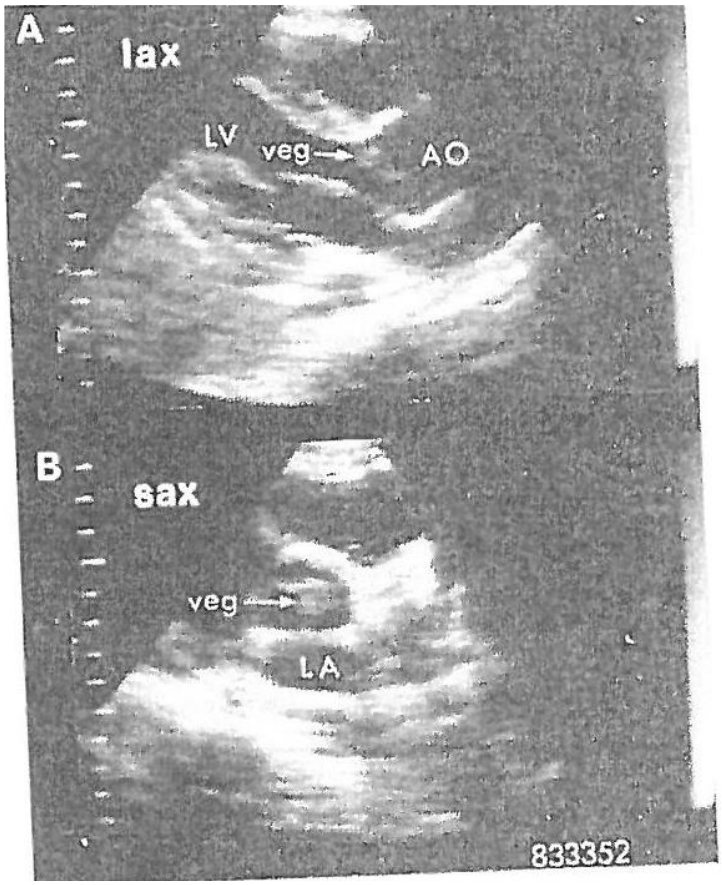


Figure 8: Long-axis and short-axis two-dimensional echocardiograms of a patient with a vegetation on the aortic valve. LV=left ventricle; AO=aorta; LA=left atrium; lax=long axis; sax=short axis (Evangelista et al., 2004).

The larger, more mobile vegetations are spectacular in real-time two-dimensional echocardiographic examination. A tricuspid valve vegetation is illustrated in Figure 9.

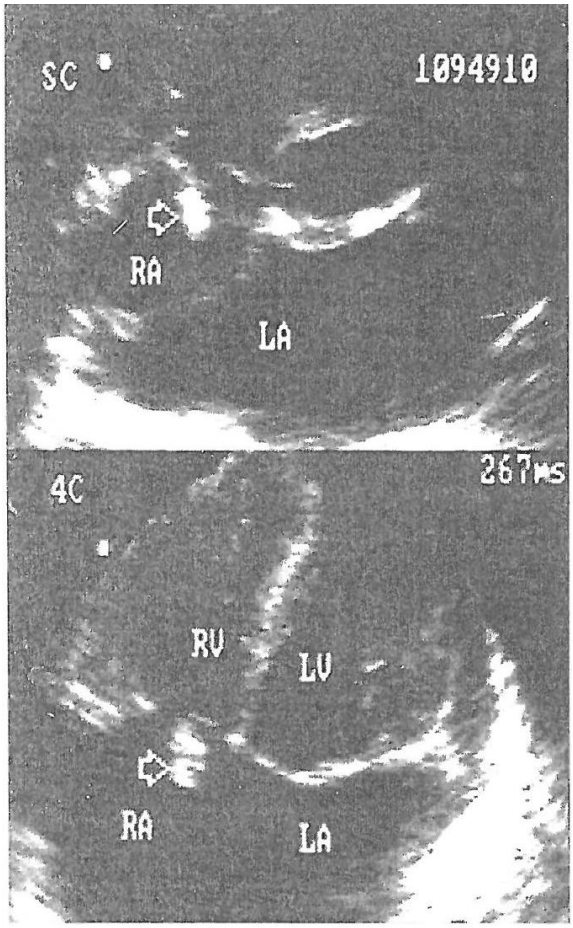


Figure 9: Subcostal (SC) and four-chamber (4C) two-dimensional echocardiograms of a patient with a vegetation on a tricuspid valve. A=right atrium; LA=left atrium; RV=right ventricle; LV=left ventricle (Fuster et al., 2009).

Figure 10 provides a two-dimensional echocardiogram of a patient who had vegetations on both the aortic valve (avv) and the mitral valve (mvv).

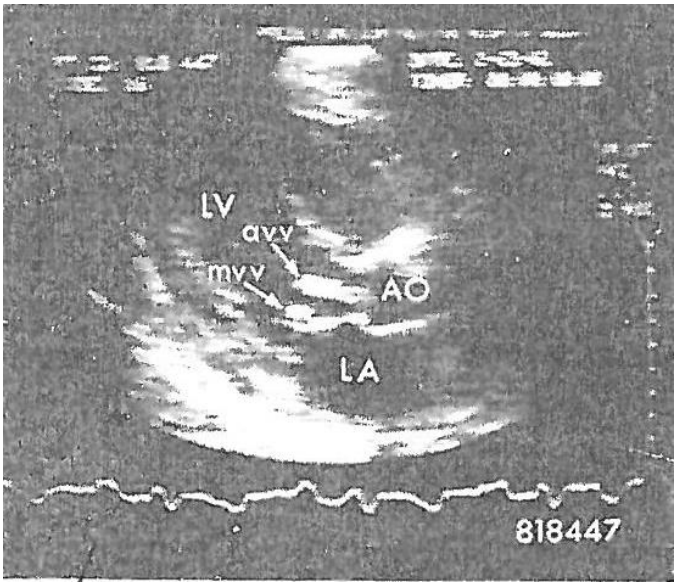


Figure 10: Long-axis two-dimensional echocardiogram of a patient with an aortic valve vegetation (avv) and a vegetation on the anterior mitral leaflet (mvv). LV=left ventricle; AO=aorta; LA=left atrium (Durack et al., 1994).

2.2 LITERATURE REVIEW

2.2.1 MICROBIOLOGY OF INFECTIVE ENDOCARDITIS

2.2.1.1 Gram-positive cocci

2.2.1.1.1Staphylococci

Infective endocarditis may be caused by staphylococci that are coagulase positive (*S aureus*) or coagulase negative (*S epidermidis* and various other species) (Cabell et al., 2003). Traditionally, it has been believed that coagulase-positive staphylococci cause primarily native valve endocarditis, whereas coagulase-negative staphylococci (CoNS) are thought to cause primarily prosthetic valve endocarditis, but considerable overlap exists (Cabell et al., 2003).

In a recent multicentre, prospective, observational investigation involving >1000 consecutive patients with definite IE from >20 countries, *S aureus* was the most common cause of prosthetic valve IE (25.8% of 214 cases), whereas 64 (8%) cases of native valve endocarditis resulted from CoNS (Cabell et al., 2003). Thus, it is important to consider both pathogens when a patient with suspected endocarditis has a preliminary blood culture that suggests staphylococci by Gram's stain interpretation.

Streptococci and staphylococci account for 80% of cases of IE, with proportions varying according to valve (native vs. prosthetic), source of infection, patient age and coexisting conditions (Figure 11).

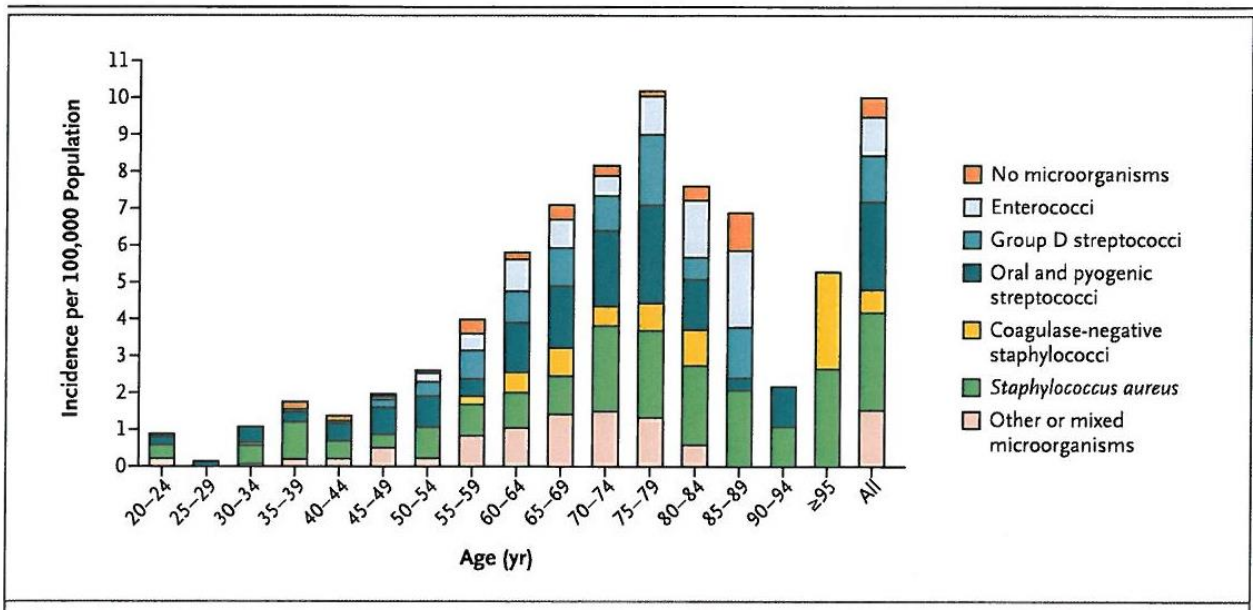


Figure 11: Incidence of definite infective endocarditis. The clustering of various predisposing factors with age probably explains the higher incidence of infective endocarditis in person 65 years of age or older (Selton-Suty et al., 2012).

Staphylococci are now the most frequently identified micro-organisms in several types of IE that result from the increased proportion of health care-associated cases of IE. In parallel, the incidence of cases attributable to oral streptococci has decreased in industrialised countries (Selton-Suty et al., 2012).

Cases of IE in which a blood culture is negative (10% of cases) may reflect one of two situations: IE in patients exposed to antibiotic agents before the diagnosis of IE or IE caused by fastidious micro-organisms (Durack et al., 1994). In the latter case, serologic testing, valve or blood polymerase chain reaction (PCR) assay, and highly specialised microbiologic techniques lead to the identification of the pathogen in 60% of cases with the most frequent micro-organisms being bartonella species, brucella species, *Coxiella burnetii* (the agent causing Q fever), bacteria in the HACEK group and *Tropheryma whipplei* (Durack et al., 1994).

Mylonakius (2001) have found that staphylococci, particularly *S.aureus,* have surpassed *streptococci viridans* as the most common cause of IE (Table 2).

Table 2: Microbiologic features of native and prosthetic valve endocarditis (Mylonakius, 2001).

PATHOGEN	NATIVE-VALVE ENDOCARDITIS				PROSTHETIC-VALVE ENDOCARDITIS		
	NEONATES	2 MO–15 YR OF AGE	16–60 YR OF AGE	>60 YR OF AGE	EARLY (<60 DAYS AFTER PROCEDURE)	INTERMEDIATE (60 DAYS–12 MO AFTER PROCEDURE)	LATE (>12 MO AFTER PROCEDURE)
	approximate percentage of cases						
Streptococcus species	15–20	40–50	45–65	30–45	1	7–10	30–33
Staphylococcus aureus	40–50	22–27	30–40	25–30	20–24	10–15	15–20
Coagulase-negative staphylococci	8–12	4–7	4–8	3–5	30–35	30–35	10–12
Enterococcus species	<1	3–6	5–8	14–17	5–10	10–15	8–12
Gram-negative bacilli	8–12	4–6	4–10	5	10–15	2–4	4–7
Fungi	8–12	1–3	1–3	1–2	5–10	10–15	1
Culture-negative and HACEK organisms*	2–6	0–15	3–10	5	3–7	3–7	3–8
Diphtheroids	<1	<1	<1	<1	5–7	2–5	2–3
Polymicrobial	3–5	<1	1–2	1–3	2–4	4–7	3–7

*Patients whose blood cultures were rendered negative by prior antibiotic treatment are excluded. HACEK denotes haemophilus species (*Haemophilus parainfluenzae, H. aphrophilus,* and *H. paraphrophilus*), *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae.*

In addition, the most common pathogens in early prosthetic-valve endocarditis, have also been well documented as an occasional cause of native-valve endocarditis. One species of community-acquired coagulase negative staphylococcus, *S. lugdunensis,* is commonly associated with valve destruction and the requirement for valve replacement (Mylonakius, 2001). The most common streptococci isolated from patients with endocarditis remain *Streptococcus sanguis, Strep. bovis, Strep. mutans* and *Strep. Mitis.* Infective Endocarditis caused by *Strep. bovis*is is prevalent among the elderly and is associated with pre-existing colonic lesions (Berlin et al., 1995).

Enterococci are frequently implicated in nosocomial bacteraemias and in IE that is resistant to medical therapy (Berlin et al.,1995). However, enterococcal endocarditis is much less common than enterococcal bacteraemia; the frequency of IE is less than 10% among patients with enterococcal bacteraemia (Berlin et al., 1995).

Polymicrobial IE, although still uncommon, is encountered most often in association with injection-drug use (Hoen et al., 1995). New diagnostic approaches, including culture and microbiologic assessment of vegetations, have yielded better understanding of blood culture negative IE (Fernandez-Guerrero et al., 1995).

Suppression of bacteraemia often persists longer than the antibiotics present in blood. Such suppression can be encountered in patients with sub-acute endocarditis by delaying empirical therapy and obtaining additional blood cultures (Fernandez-Guerrero et al., 1995). The polymerase chain reaction (PCR) can be used to identify unculturable organisms and excised vegetations or systemic emboli (Hoen et al., 1995).

Only 5-7% of patients who have been given a diagnosis of IE according to strict criteria and who have not recently received antibiotics will have sterile blood cultures. For example, blood cultures were found to be negative in 88 of 620 cases (14%) of IE documented in France during a one-year nationwide survey (Brouqui et al., 2001). In 42 of 88 cases, negative cultures were associated with the administration of antibiotics before blood was drawn for culture (Brouqui et al., 2001).

This approach has been used to diagnose IE due to *Tropherym whipplei* and bartonella species and is a promising tool for establishing a microbiologic diagnosis in selected patients with blood-culture-negative IE (Goldenberger et al., 1997). When blood cultures from patients with suspected IE remain sterile after 48 to 72 hours of incubation, the clinician must advise the laboratory of the suspected diagnosis. This will allow the laboratory, if the blood cultures remain negative after five to seven days, to intensify efforts to recover fastidious organisms and initiate serologic assessment of causation (Goldenberger et al., 1997).

Use of the lysis centrifugation system for blood cultures allows direct to special supportive mediums, with the potential to increase the speed of recovery of more fastidious organisms. These efforts could include prolonged incubation and the planting of subcultures on more enriched mediums (Bayer et al., 1998).

2.2.1.1.2 *Staphylococcus aureus*

Staphylococcus aureus (S aureus) is the most common cause of IE in much of the developed world. This increase is primarily a consequence of healthcare contact (e.g., intravascular catheters, surgical wounds, indwelling prosthetic devices). Increasing rates of oxacillin resistance in both hospital and community settings and the recovery of clinical *S aureus* isolates both partially and fully resistant to vancomycin have complicated the treatment of *S aureus* endocarditis. In non-addicts, endocarditis arising from *S aureus* primarily involves the left side of the heart and is associated with mortality rates ranging from 25-40% (Cabell et al., 2002).

2.2.1.1.3 Enterococci

Enterococci, which belong to Lancefield's group D, are no longer designated as part of the *Streptococcus* genus but have a separate genus, *Enterococcus*. Although there are >15 species within the *Enterococcus* genus, *E faecalis* and *E faecium* are the major species isolated from clinical sources (Cabell et al., 2002).

In comparison with Streptococci, enterococci are relatively resistant to penicillin, ampicillin and vancomycin. Streptococci are usually killed by these antimicrobials alone, whereas enterococci are inhibited but not killed. Killing of susceptible strains of enterococci requires the synergistic action of penicillin, ampicillin or vancomycin in combination with either gentamicin or streptomycin (Cabell et al., 2002).

Enterococci are relatively impermeable to aminoglycosides. High concentrations of aminoglycosides in the extracellular milieu are required to achieve sufficient concentrations of the drug at the site of the ribosomal target within the bacterial cell for bactericidal activity (Bayer et al.,1998). These concentrations are higher than can be achieved safely in patients; however, cell-wall-active agents such as penicillin, ampicillin and vancomycin raise the permeability of the enterococcal cell so that a bactericidal effect can be achieved by concentration of an aminoglycoside, which is readily achieved in patients without excessive toxicity (Bayer et al., 1998).

If an enterococcus strain is resistant to the cell-wall-active agent or high concentrations of an aminoglycoside (500 µg/mL of gentamicin or 1000 µg/mL of streptomycin), then the combination of an aminoglycoside with the cell-wall-active agent will not result in bactericidal activity *in vitro* or *in vivo* (animal model of endocarditis), nor will it predictably produce a microbiological cure in human enterococcal endocarditis (Cabell et al., 2002).

Results of studies of experimental enterococcal endocarditis suggest that an *in vivo* post-antibiotic effect does not occur with penicillin, ampicillin or vancomycin (Cabell et al., 2002). Some animal model data suggest that continuous infusion of a β-lactam is more effective than is intermittent infusion, whereas other studies suggest an equivalent effect (Cabell et al., 2002).

2.2.1.1.3.1 Enterococci susceptible to penicillin, vancomycin and aminoglycoside

When combined with penicillin or ampicillin, streptomycin and gentamicin therapy had similar microbiological cure rates for enterococcal endocarditis (Mandell et al., 1970). The choice of a specific aminoglycoside for therapy should be based on gentamicin and streptomycin *in vitro* susceptibility testing (Mandell et al., 1970). If the strain is susceptible to both gentamicin and streptomycin, then gentamicin is preferred because the determination of serum gentamicin concentrations may be performed in most laboratories, whereas streptomycin serum concentrations require special laboratory testing (Mandell et al.,1970)

Single daily dosing of aminoglycosides compared with dosing every eight hours in animal models of enterococcal endocarditis have yielded conflicting results (Rice et al., 1991). These results may reflect different pharmacokinetics of aminoglycosides in animals as compared with humans (Mandell et al.,1970). Until more data demonstrate that once-daily dosing of an aminoglycoside is as effective as multiple dosing, gentamicin or streptomycin should be administered in daily multiple divided doses rather than a daily single dose to patients with enterococcal endocarditis (Mandell et al., 1970).

The duration of antimicrobial therapy in native valve endocarditis depends on the duration of infection before diagnosis and onset of effective therapy. Patients with <3 months' duration of symptoms may be treated successfully with four weeks of antimicrobial therapy, whereas patients with ≥3 months' duration of symptoms require six weeks of therapy. Patients with prosthetic valve endocarditis should receive at least six weeks of antimicrobial therapy (Rice et al., 1991).

In patients with normal renal function, gentamicin should be administered every eight hours and the dosage adjusted to achieve a one-hour serum concentration of 3 μg/mL and at concentration of <1 μg/mL. Increasing the dosage of gentamicin in these patients did not result in enhanced efficacy but did increase the risk of nephrotoxicity (Geraci,1958). In patients with mildly abnormal renal function (creatinine clearance ≥50 mL/min), the dosage of gentamicin should be adjusted and the serum concentrations closely monitored to achieve the above target concentrations. In patients with more severely reduced renal function (creatinine clearance <50 mL/min), treatment should be in consultation with an infectious diseases specialist (Geraci, 1958).

Vancomycin therapy should be administered only if a patient is unable to tolerate penicillin or ampicillin. Combinations of penicillin or ampicillin with gentamicin are preferable to combined vancomycin-gentamicin because of the potential increased risk of totoxicity and nephrotoxicity with the vancomycin-gentamicin combination. Moreover, combinations of penicillin or ampicillin and gentamicin are more active than combinations of vancomycin and gentamicin *in vitro* and in animal models of experimental endocarditis. Patients with native valve endocarditis should receive six weeks of vancomycin-gentamicin therapy; patients with prosthetic valve infection should also receive at least six weeks of therapy (Geraci,1958).

2.2.1.2 Culture-negative endocarditis

Positive blood cultures are a major diagnostic criterion for IE and key to identifying the etiologic agent and the optimal antimicrobial regimen (Werner et al., 1967). Continuous bacteraemia and a high frequency of positive blood cultures are typical of this infection. In a study of 206 patients with blood-culture-positive endocarditis, 95% of 789 blood cultures yielded the causative micro-organism, and in 91% of cases, all of the cultures were positive (Werner et al.,1967). The intensity of bacteraemia may not be great, however; <50 colony-forming units per millilitre of blood were detected in the majority of patients (Werner et al., 1967).

Blood cultures are negative in up to 20% of patients with IE diagnosed by strict diagnostic criteria. Failure to culture the micro-organism causing endocarditis may result from inadequate microbiological techniques, infection with highly fastidious bacteria or nonbacterial pathogens, or previous administration of antimicrobial agents before the blood was obtained (Table 3) (Mylonakius, 2001).

Table 3: Laboratory diagnosis of negative endocarditis (Mylonakius, 2001).

ORGANISM	APPROACH
Abiotrophia species (previously classified as nutritionally variant streptococci)	Grow in thioglycolate medium of blood culture and as satellite colonies around *Staphylococcus aureus* on blood agar or on medium supplemented with pyridoxal hydrochloride or L-cysteine
Bartonella species (usually *Bartonella henselae* or *B. quintana*)	Serologic tests Lysis-centrifugation system for blood cultures PCR of valve or embolized vegetations[25,28,29]; special culture techniques available, but organisms are slow-growing and may require a month or more for isolation
Coxiella burnetii (Q fever)	Serologic tests PCR, Giemsa stain, or immunohistologic techniques on operative specimens
HACEK organisms	Blood cultures positive by day 7; occasionally require prolonged incubation and subculturing
Chlamydia species (usually *Chlamydia psittaci*)	Culture from blood has been described Serologic tests Direct staining of tissue with use of fluorescent monoclonal antibody
Tropheryma whipplei	Histologic examination (silver and PAS stains) of excised heart valve; PCR[26] or culture of vegetation[30]
Legionella species	Subculture from blood cultures, lysis-centrifugation pellet from blood cultures, or operative specimens on BCYE agar; direct detection on heart valves with fluorescent antibody Serologic tests
Brucella species (usually *Brucella melitensis* or *B. abortus*)	Serologic tests Prolonged incubation of standard or lysis-centrifugation blood cultures
Fungi	Regular blood cultures often positive for candida species; lysis-centrifugation system with specific fungal medium can increase yield; testing urine for *Histoplasma capsulatum* antigen or serum for *Cryptococcus neoformans* polysaccharide capsular antigen can be helpful Accessible lesions (such as emboli) should be cultured and examined histologically for fungi

*PCR denotes polymerase chain reaction; HACEK organisms haemophilus species (*Haemophilus parainfluenzae, H. aphrophilus,* and *H. paraphrophilus*), *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae;* PAS periodic acid–Schiff; and BCYE buffered charcoal yeast extract.

The last of these three factors is an important cause of culture-negative endocarditis because it is so prevalent.

Administration of antimicrobial agents to IE patients before blood cultures are obtained reduces the recovery rate of bacteria by 35-40% (Pazin et al., 1982). Endocarditis patients with blood cultures that are initially negative after only a few days of antibiotic therapy may have positive blood cultures after several days without antibiotics (Pazin et al., 1982).

Patients should be classified into one of two groups (provided the reason for negative blood cultures is determined not to be inadequate laboratory techniques) when choice of empirical therapy is considered. One group includes patients who received antibiotic therapy before collection of blood cultures. For those with acute clinical presentation of native valve infection, coverage for *S aureus* should be provided as outlined in the section on the treatment of proven staphylococcal disease. For patients with subacute presentation, coverage of *S aureus*, *Streptococci viridans*, and *enterococci* should be given. Patients with culture-negative prosthetic valve infection should receive vancomycin if the onset of symptoms occurs within one year of prosthetic valve placement to provide coverage of oxacillin-resistant staphylococci (Mylonakius, 2001).

2.2.1.3 Gram-negative cocci

Neisseria gonorrhoeae was responsible for at least 5-10% of IE cases before the introduction of penicillin but it is rarely implicated (Weiss et al., 1992). Of the cases of gonococcal endocarditis reported since 1949, most occurred in young men (Jackman et al., 1991). Skin manifestations consistent with the gonococcal arthritis-dematitis syndrome endocarditis was documented in only 20% of cases. Most cases of gonococcal endocarditis follow an indolent course in contrast to the often fulminant progression in the pre-antibiotic era (Jackman et al., 1991).

Aortic valve involvement, large vegetations seen on TTE, associated valve ring abscesses and nephritis are common (Weiss et al.,1992). Sudden haemodynamics deterioration despite appropriate therapy may occur and the mortality rate remains at 20% (Jackman et al.,1991). A high frequency of late–complement component deficiencies has been noted in patients with gonococcal endocarditis (Jackman et al., 1991).

The gonococci that cause systemic infection are usually susceptible to penicillin. Infective Endocarditis caused by these organisms as well as by meningococci can be effectively treated with the same penicillin regimen recommended for pneumococcal

endocarditis. There are several reasons why infectious disease consultation should be obtained in cases in which gonococci are resistant to penicillin. These include limited clinical experience and various mechanisms of penicillin resistance to other potential therapies, including ceftriaxone and ciprofloxacin (Weiss et al., 1992).

2.2.1.4 Fungi

Fungal endocarditis is a relatively new syndrome and is often a complication of medical and surgical advances. Despite aggressive combined medical and surgical interventions, mortality rates for fungal endocarditis are unacceptably high. The survival rate for patients with mould-related endocarditis is <20%. Patients who develop this illness usually have multiple predisposing conditions that often include the use of cardiovascular devices, in particular prosthetic cardiac valves and central venous catheters (Pierrotti et al., 2002).

Candida and *Aspergillus* species account for the large majority of fungal endocarditis infections, and *Candida*-related endocarditis is much more common than *Aspergillus*-related disease. Blood cultures are usually positive when caused by the former pathogen, whereas they are rarely positive in cases caused by the latter fungus. Aspergillusis is a cause of culture-negative endocarditis, and when it occurs, it is usually in a patient with recent placement of a prosthetic cardiac valve (Pierrotti et al., 2002).

Historically two treatment have prevailed in fungal endocarditis, despite the lack of prospective trials conducted to define the most appropriate therapy (Pierrotti at al., 2002). Fungal endocarditis is a stand-alone indication for surgical replacement of an infected valve. The second is that amphotericin B, a fungicidal agent, is the drug of choice for fungal endocarditis. In view of the availability of newer antifungal drugs, a re-evaluation of these principles seems in order. If done, however, it will be based on anecdotal experience and expert opinion rather than on clinical data because of the rarity of the syndrome (Pierotti et al., 2002).

A two-phase therapy has evolved in 18 years ago (Nguyen et al., 1996). The initial or induction phase consists of control of infection. Treatment is a combination of a parenteral antifungal agent, usually an amphotericin B-containing product and valve replacement. If the patient survives, the antifungal therapy is usually given for >/ 6 weeks (Nguyen et al., 1996). After a clinical response to initial induction therapy, long-term suppressive therapy with an oral azole has been used (Nguyen et al., 1996).

Firstly, because of the high relapse rate of fungal endocarditis and the prolonged delay in relapse, oral azole has been administered after combined medical and surgical induction therapy. Secondly, with fungal endocarditis, lifelong oral antifungal suppressive therapy has been given to patients who respond clinically to induction medical therapy but are not deemed appropriate surgical candidates for valve replacement as an attempted infection cure. Anecdotal case series indicate that infection has been successfully suppressed for months to years (Nguyen et al., 1996).

2.2.2 COMPLICATIONS

2.2.2.1 Congestive heart failure

Many studies prior to 2003 have demonstrated that among the complications of IE, congestive heart failure (CHF) has the greatest impact on prognosis (Vikram et al., 2003). Moderate to severe CHF was identified as one of five baseline features that were independently associated with six-month mortality in an investigation to validate a prognostic classification system for adults with complicated left-sided native valve IE. In native valve IE, acute CHF occurs more frequently in aortic valve infections (29%) than with mitral (20%) or tricuspid disease (8%) (Moon et al., 1997).

The degree of tolerance of CHF is valve-dependent, with acute aortic regurgitation being least tolerant and acute tricuspid regurgitation being most tolerant. Congestive heart failure may develop acutely from perforation of a native or bioprosthetic valve leaflet, rupture of infected mitral chordate, valve obstruction by bulk vegetations or sudden intracardiac shunts from fistulous tracts or prosthetic dehiscence. Mitral valve preclosure that can be detected by both physical examination and echocardiography should be screened for in each case (Vikram et al., 2003).

Congestive heart failure also may develop more insidiously despite administration of appropriate antibiotics as a result of progressive worsening of valvular insufficiency and ventricular dysfunction. Patients who have normal ventricular function or only mild CHF when IE is initially diagnosed may progress to severe CHF during treatment and two-thirds of these patients will do so within the first month of therapy (Moon et al., 1997).

Echocardiographic evaluation of IE patients delineates the causes and severity of CHF. Ventricular size, wall motion and dynamic function can be readily defined and valve insufficiency quantified. Progressive chamber enlargement, elevation of pulmonary arterial pressures and increasing wall stress on serial evaluation indicate a trend toward decompensation. Medical and surgical treatment decisions can be guided by echocardiographic detection of fistulae, prosthetic dehiscence, obstructive vegetations, or flail leaflets (Moon et al., 1997).

Surgical approaches to IE patients with CHF must take into account the distortion of the valve and its surrounding structures. Severe valvular disruption will usually require prosthetic replacement. Ruptured mitral chordate may sometimes be repaired with a combination of leaflets resection, chordal reattachment or transposition of an annular support. Leaflet perforations may be repaired with small pericardial patches if the surrounding leaflet tissue is well preserved and valve motion can be maintained. Discrete vegetations on aortic or mitral leaflets have been excised along with underlying leaflet tissue and repaired with a patch (Mugge et al., 1989).

2.2.2.2 Risk of embolisation

Systemic embolisation occurs in 22-50% of cases of IE. Emboli often involve major arterial beds, including the lungs, coronary arteries, spleen, bowel and extremities. Up to 65% of embolic events involve the central nervous system and >90% of central nervous system emboli lodge in the distribution of the middle cerebral artery. The highest incidence of embolic complications is seen with aortic and mitral valve infections and in IE caused by *S aureus, Candida* and *Abiotrophia* organisms. Emboli can occur before diagnosis, during therapy or after therapy has been completed, although most emboli occur within the first two to four weeks of antimicrobial therapy (Mugge et al., 1989).

The embolic rate dropped from 13 to <1.2 embolic events per 1000 patient-days during that time, confirmed the reduction in frequency of embolisation after two weeks of therapy. Moreover, the latter re-emphasised the increased risk of embolisation with increasing vegetation size during therapy, mitral valve involvement and staphylococcal causes. Prediction of individual patient risk for embolisation is extremely difficult. Many studies have attempted to use echocardiography to identify a high-risk subset of IE patients who might benefit from early surgery to avoid embolisation (Vilacosta et al., 2002).

TTE have demonstrated a trend toward higher embolic rates with left-sided vegetations >1 cm in diameter. It compared TTE with multiplane TEE and found that neither technique was helpful in defining embolic risk in patients with vegetations (Heinle et al., 1994). Mitral vegetations >1 cm in diameter were associated with the greatest frequency of embolism. The association was strengthened when analysis was limited to those patients who had not yet experienced a clinical embolic event. Another prospective study, however, found no clear correlation of vegetation size with embolisation (Konstadt et al., 1994).

Overall are compatible with that indicate that in general, mitral vegetations of any size are associated with a higher risk of embolisation (25%) than aortic vegetations (10%).The highest embolic risk (37%) has been seen in the subset of patients with mitral vegetations attached to the anterior rather than the posterior mitral leaflet (Konstadt et al., 1994). The effect of vegetation size on embolic potential was dependent on the infecting organism, with large vegetations independently predicting embolic events only in the setting of streptococcal IE. In contrast, as confirmed above by Vilacosta et al., (2002), staphylococcal or fungal IE appears to carry a high incidence rate of embolisation independent of vegetation size (Vilacosta et al., 2002).

The role of echocardiography in predicting embolic events has been controversial. In one survey (Heinle et al., 1994) that included four echocardiographers who had no access to clinical data, interobserver agreement was mixed on the characterisation of vegetations. Agreement was high for the presence of vegetation (98%) and site involved (97%); interobserver agreement was considerably less for vegetation size (73%), mobility (57%), shape (73%) and attachment (40%) (Heinle et al., 1994).

An embolic event was one of four early predictors of in-hospital death caused by IE (Chu et al., 2004). Other independent predictors of death by logistic regression modelling among 267 consecutive patients with definite or possible IE, by modified Duke criteria, were diabetes mellitus and *S aureus* infection (Chu et al., 2004). An increase in vegetation size over four to eight weeks of therapy as documented by TEE does appear to predict embolic events (Chu et al., 2004). In addition a second, albeit infrequent, peak of late embolic events has been observed to occur 15 to 30 weeks after diagnosis of IE and has been associated with non-healing vegetations as defined by echocardiography (Chu et al., 2004).

2.2.2.3 Periannular extension of infection

Extension of IE beyond the valve annulus predicts a higher mortality rate, more frequent development of CHF and more frequent cardiac surgery. Perivalvular cavities form when annular infections break through and spread into contiguous tissue. In native aortic valve IE, this generally occurs through the weakest portion of the annulus, which is near the membrane septum and atrioventricular node (Alsip et al., 1985). The anatomic vulnerability of this area explains both why abscesses occur in this location and why heart block is a frequent sequel. Periannular extension is a common occurrence in 10-40% of all native valve IE, and complicating aortic IE occurs more commonly than mitral or tricuspid IE (Alsip et al., 1985). Periannular infection is of even greater concern with prosthetic valve IE, occurring in 56-100% of patients. Perivalvular abscesses are particularly common with prosthetic valves because the annulus, rather than the leaflet, is the usual primary site of infection. Most periannular infections involving the mitral area are associated with prosthetic mitral valves (Alsip et al., 1985).

Under the influence of systemic intravascular pressures, abscesses may progress to fistulous tracts that create intracardiac or pericardial shunts. The mortality rate was 41% in one series of patients with aorto-cavitary fistulisation despite surgical intervention in 87% (Chan et al., 2003). Multivariate analysis demonstrated that factors associated with an increased risk of death included moderate to severe heart failure, prosthetic valve involvement and urgent or emergency surgical intervention (Chan et al., 2003). In progressive periannular infection totally disrupts the ventricular-aortic continuity or the mitral-aortic trigone (Chan et al., 2003). Such structural lesions and intracardiac fistulae may be catastrophic; even if their haemodynamic impact is tolerated, such lesions will not heal with medical treatment alone and require urgent operative intervention (Chan et al., 2003).

Clinical parameters for the diagnosis of perivalvular extension of IE are inadequate. Persistent bacteraemia or fever, recurrent emboli, heart block, CHF, or a new pathological murmur in a patient with IE on appropriate antibiotics may suggest extension (Middlemost et al., 1991). Only aortic valve involvement and recent injection drug use have been prospectively identified as independent risk factors for perivalvular abscess. On an electrocardiogram (ECG), new atrioventricular block has a positive predictive value of 88% for abscess formation but low (45%) sensitivity (Middlemost et al., 1991).

Patients at risk of perivalvular extension of IE require prompt evaluation. The size of vegetations is not helpful for predicting perivalvular extension. The sensitivity of TTE for detecting perivalvular abscess is low (18-63% in prospective and retrospective studies, respectively). Transoephageal Echocardiography dramatically improves sensitivity for defining periannular extension of IE (76-100%) while retaining excellent specificity (95%) and positive and negative predictive values (87% and 89%, respectively) (Middlemost et al., 1991).

When combined with spectral and colour Doppler techniques, TEE can demonstrate the distinctive flow patterns of fistulae and pseudo-aneurysms and can rule out communications from unruptured abscess cavities. Because of these combined capabilities, TEE is the modality of choice for the initial assessment of any patient suspected of having perivalvular extension of IE (Class I, Level of Evidence: A) (Rohmann et al., 1991).

A small number of patients with periannular extension of infection or myocardial abscess may be treated successfully without surgical intervention. These patients potentially include those who have smaller (<1 cm) abscesses and who do not have complications such as heart block, echocardiographic evidence of progression of

abscess during therapy, valvular dehiscence, or insufficiency. Such patients should be monitored closely with serial TEE; TEE should be repeated at intervals of two, four, and eight weeks after completion of antimicrobial therapy (Vlessis et al., 1996). Surgery for patients with perivalvular extension of IE is directed at radication of the infection, as well as correction of haemodynamic abnormalities. Drainage of abscess cavities, excision of necrotic tissue and closure of fistulous tracts often accompany valve replacement surgery (Vlessis et al., 1996).

Although valve replacement is usually required, it may be complicated in the face of extensive destruction of the periannular supporting tissues. Under these conditions, human aortic homografts, when available, can be used to replace the damaged aortic valve, as well as to reconstruct the damaged aorta. Homografts have a constant but low incidence rate of development of sewing-ring infections and mural IE, possibly related to the improved penetration of antibiotics. Some groups have recently advocated the use of “stentless” or “mini-stented” aortic valve prostheses with debridment in the same clinical scenario, particularly if homografts are not readily available (Walkes et al., 2003).

2.2.2.4 Splenic abscess

Splenic abscess is a well-described but rare complication of IE. This infection develops by one of two mechanisms: bacteraemic seeding of a bland infarction, created via splenic arterial occlusion by embolised vegetations, or direct seeding of the spleen by an infected embolus also originating from an infected valvular vegetation. Although splenic infarction is a common complication of left-sided IE (40% of cases), it is estimated that only ≈5% of patients with splenic infarction will develop splenic abscess (Robinson et al., 1992).

Reflecting their overall high frequencies in IE, viridans streptococci and *S aureus* each account for ≈40% of cases in which splenic abscess cultures are positive, whereas enterococci account for 15% of cases. Aerobic Gram-negative bacilli and fungi are isolated in <5% of cases. Clinical splenomegaly, which is present in up to 30% of cases of IE, is not a reliable sign of splenic infarction or abscess (Robinson et al., 1992).

Splenic infarction delineated by imaging techniques often causes asymptomatic pain in the back, left flank, or left upper quadrant, or abdominal tenderness may be associated with either splenic infarction or abscess. Splenic rupture with haemorrhage is a rare complication of infarction. Persistent or recurrent bacteraemia, persistent fever, or other signs of sepsis are suggestive of splenic abscess. Patients with these findings should be evaluated via one or more of the imaging studies discussed below (Robinson et al., 1992).

On ultrasonography, ^{99m}Tc liver-spleen scans, labelled white blood cell scans and gallium scans have become obsolete in the diagnosis of splenic abscess. Differentiation of splenic abscess from bland infarction may be difficult. Infarcts are generally associated with clinical and radiographic improvement during appropriate antibiotic therapy. Definitive treatment is splenectomy with appropriate antibiotics, and this should be performed immediately unless urgent valve surgery is also planned. Percutaneous drainage or aspiration of splenic abscess has been performed successfully and this procedure may be an alternative to splenectomy for the patient who is a poor surgical candidate (Robinson et al., 1992). The use of laparoscopic splenectomy has been emphasized as an alternative to formal laparotomy approaches (Robinson et al., 1992). If possible, splenectomy should be performed before valve replacement surgery to mitigate the risk of infection of the valve prosthesis as a result of the bacteraemia from the abscess (Simsir et al., 2003).

2.2.2.5 Mycotic aneurysms

Mycotic aneurysms (MAs) are uncommon complications of IE that result from septic embolisation of vegetations to the arterial vasa vasorum or the intraluminal space, with subsequent spread of infection through the intima and outward through the vessel wall. Arterial branching points favour the impaction of emboli and are the most common sites of development of mycotic aneurysms. Mycotic aneurysms caused by IE occur most frequently in the intracranial arteries, followed by the visceral arteries and the arteries of the upper and lower extremities (Francioli, 1991).

2.2.2.6 Intracranial mycotic aneurysms (ICMAs)

Neurological complications develop in 20-40% of patients with IE. Intracranial MAs (ICMAs) represent a relatively small but extremely dangerous subset of these complications. The overall mortality rate among IE patients with ICMAs is 60%. Among patients with unruptured ICMAs, the mortality rate is 30%; in patients with ruptured ICMAs, the mortality rate approaches 80%.The distal middle cerebral artery branches are most often involved, especially the bifurcations. Intracranial mycotic aneurysms occur in 20% of cases; mortality rates are similar for multiple or single distal ICMAs. The mortality rate for patients with proximal ICMAs is >50% (Moskowitz et al., 1974).

The clinical presentation of patients with ICMAs is highly variable. Patients may develop severe headache, altered sensorium, or focal neurological deficits such as hemianopia or cranial neuropathies; neurological signs and symptoms are nonspecific and may suggest a mass lesion or an embolic event. Some ICMAs leak slowly before rupture and produce mild meningeal irritation (Bohmfalk et al., 1978). Frequently, the spinal fluid in these patients is sterile, and it usually contains erythrocytes, leukocytes and elevated protein. In other patients, there are no clinically recognised premonitory findings before sudden subarachnoid or intraventricular haemorrhage (Bohmfalk et al., 1978).

In the absence of clinical signs or symptoms of ICMAs, routine screening with imaging studies is not warranted (Bohmfalk et al.,1978). Symptomatic cerebral emboli frequently, but not invariably, precede the finding of an ICMA. Accordingly, imaging procedures to detect ICMAs are indicated in IE patients with localised or severe headaches; “sterile” meningitis, especially if erythrocytes or xanthochromia is present; or focal neurological signs (Bohmfalk et al., 1978).

Noncontrast computed tomography (CT) may provide useful initial information in patients who are suspected of having an ICMA. This technique has a sensitivity of 90-95% for intracerebral bleeding and may indirectly identify the location of the MA. Magnetic resonance angiography (MRA; non-contrast or contrast-enhanced) and contrast-enhanced computed tomography angiography (CTA) are non-invasive methods used to detect ICMAs. Although these methods may someday replace conventional catheter angiography, they should be considered screening techniques (Huston et al.,1994). CTA can be performed more rapidly than MRA, although the contrast load may be substantial, which is a significant concern in patients with renal insufficiency and/or CHF. These methods have similar sensitivity and specificity (90-95%) for detecting ICMAs, although rapid improvements in technology continue to advance both techniques. Both techniques are also far less accurate in identification of small (<5 mm) aneurysms (Huston et al., 1994).

Conventional cerebral angiography remains the diagnostic imaging test for diagnosing ICMAs. The accuracy of this method has been enhanced by the use of a three-dimensional rotation technique that improves spatial resolution in comparison with conventional two-dimensional technology. In most cases, magnetic resonance imaging (MRI)/MRA or CT/CTA can provide sufficient information to identify and monitor intracranial aneurysms (Bingham et al.,1977). Conventional angiography is required when suspicion remains and the results of less-invasive studies are negative, particularly in the context of small (≤5 mm) ICMAs (Bingham et al., 1977).

Intracranial mycotic aneurysms may heal with medical therapy. Bingham et al., (1977) reported that ICMAs resolved between initial and follow-up angiography in 52% of patients treated with effective antibiotic therapy. A decrease in ICMA size was observed in an additional 29% of patients. In 19% of patients, however, ICMA increased in size by the time of the second angiogram, and in 10% a new ICMA was discovered. Although it is clear that in many patients ICMAs treated with antibiotics alone will heal, in others rupture may lead to significant morbidity or death (Bingham et al.,1977).

The risk of intervention is affected by the patient's age, underlying comorbid conditions and the location of the ICMA. No data precisely identify patients at risk of "imminent rupture," and decisions concerning medical versus surgical therapy must be individualised. It is generally believed that a single ICMA distal to the first bifurcation of a major artery (e.g., middle cerebral artery) should be monitored with frequent serial imaging (CTA, MRA, or conventional angiography) and treated promptly if the aneurysm enlarges or bleeds (Bingham et al.,1977).

Multiple ICMAs a complex problem and should be monitored closely. Intracranial mycotic aneurysms that occur proximally to the first bifurcation are less amenable to surgical excision. Such ICMAs frequently arise from major vessels, and ligation may result in severe neurological deficits. As with distal aneurysms, proximal lesions should be monitored with serial neuro-imaging, and if signs of enlargement or leakage develop, intervention should be strongly considered. Occasionally, proximal ICMAs stabilise and form a thrombus with antimicrobial therapy (Bingham et al., 1977).

Endovascular treatment of ICMAs has been used as an alternative to surgical clipping or ligation. The less-invasive nature of endovascular treatment is an advantage, permitting the treatment of patients who might otherwise be poor candidates for

intervention. Several case series have reported that this treatment can be used successfully in IE-related aneurysms. For example, Chapot et al., (2002) reviewed their experiences with endovascular treatment in 18 ICMAs among 14 IE patients in France; most ICMAs were located within the distal cerebral circulation. Late follow-up cerebral angiography with cyanoacrylate, autologous clots, and detachable or fibred coils showed stable aneurysm occlusion, and 10 of 14 patients experienced a normal long-term neurological outcome (Chapot et al., 2002).

Some patients with IE require both cardiac valve replacement and ICMA ligation. Although data are limited in this situation, an approach that uses staged procedures, with the more severe problem dictating the procedure to be performed first, has been suggested. A bioprosthetic valve, which does not require that the patient receive anticoagulant therapy, may be preferable to a mechanical valve in this case. To prevent haemorrhagic complications, it has been suggested that valve surgery be delayed for a minimum of two weeks after either a central nervous system embolic event or bleed or repair of ICMAs (Chapot et al., 2002).

2.2.2.7 Extracranial mycotic aneurysms (ECMAs)

Intrathoracic or intra-abdominal MAs are often asymptomatic until leakage or rupture occurs (Mansur et al.,1986). Presumably, most extracranial MAs (ECMAs) will rupture if not excised (Mansur et al., 1986). The appearance of a tender, pulsatile mass in a patient with IE should suggest an ECMA. Haematemesis, haematobilia and jaundice suggest rupture of a hepatic artery MA; arterial hypertension and haematuria suggest rupture of a renal MA; and massive bloody diarrhoea suggests the rupture of an ECMA into the small or large bowel (Mansur et al., 1986).

Proximal and distal ligation with excision of all infected material is ideal but generally not feasible. Moreover, the risk of reinfection and rupture of interposed vascular grafts is high. Revascularisation is usually established via extra-anatomic routes through uninfected tissue planes. Autologous venous grafts have a lower risk of recurrent infection than do synthetic materials. Long-term suppressive oral antimicrobial therapy may be desirable in patients at high risk of recurrence of infection, such as those with interposed vascular grafts in infected areas (Mansur et al., 1986).

Despite improved diagnostic techniques and more aggressive surgical therapy, the mortality rate among patients with IE and ECMA is high and is attributable to suture-line infection with vessel or graft rupture. For most patients, however, surgical intervention represents the only hope for radical cure of ECMAs and an improved chance of survival (Mansur et al., 1986).

2.2.3 TREATMENT

2.2.3.1 Surgical therapy

Decisions regarding surgical intervention in patients with IE should be individualised, with input from both the cardiologist and the cardiovascular surgeon (Steckelberg et al., 1991). If a patient with IE is receiving long-term oral anticoagulant, commanding therapy, it should be discounted and replaced by heparin immediately after the diagnosis of IE has been established in the event that surgical intervention is required (Steckelberg et al., 1991).

Other clinical situations in which surgical intervention should be considered are fungal IE. Infection with aggressive antibiotic-resistant bacteria or bacteria that respond poorly to antibiotics, left-sided IE caused by Gram-negative bacteria such as *S marcescens* and *Pseudomonas* species. Persistent infection with positive blood

cultures after one week of antibiotic therapy, or one or more embolic events during the first two weeks of antimicrobial therapy (Steckelberg et al., 1991).

Patients with IE and CHF, irrespective of the mechanisms, should be evaluated immediately for possible surgical therapy. Despite a higher operative mortality rate in patients with CHF than in those without CHF, patients with IE who have CHF and undergo valve surgery have a substantially reduced mortality rate compared with those treated with medical therapy alone (Sexton et al., 2003). The incidence of reinfection of newly implanted valves in patients with active IE is 23% and is far less than the mortality rate for IE and CHF without surgical therapy, which can be as high as 51% (Sexton et al., 2003).

Consideration of surgical intervention is also warranted when there is echocardiographic evidence of valve dehiscence, perforation, rupture, or a fistula or a large perivalvular abscess. Other echocardiographic findings that indicate the possible need for surgery are anterior mitral leaflet vegetation (particularly with size >10 mm) or persistent vegetation after systemic embolisation and increase in vegetation size despite appropriate antimicrobial therapy (Steckelberg et al., 1991).

The greatest risk of embolisation appears to occur with vegetation >10mm in diameter occurring on the anterior mitral leaflets and during the first one to two weeks of therapy (Steckelberg et al., 1991). Prosthetic valve IE, particularly early prosthetic valve IE (<12 months after valve replacement), is often caused by infection by *Staphylococcus* species and may be particularly severe with perivalvular abscess and valve dehiscence (Steckelberg et al., 1991). Even in patients with prosthetic valve IE, however, decisions regarding surgical intervention are complex and depend on many individual factors that vary among patients, including infective organism, vegetation size, presence of perivalvular infection, presence of embolism or heart failure, age and non-cardiac morbidities (Steckelberg et al., 1991).

2.2.3.2 Anticoagulation

Anticoagulation in IE patients is controversial, particularly in mechanical valve endocarditis. In general in patients with native valve disease, the benefit of anticoagulant has never been demonstrated convincingly. In contrast, some authorities recommend continuation of therapy in patients with mechanical prosthetic valve IE. However, the general advice is to discontinue all anticoagulation in patients with *S aureus* prosthetic valve IE who have experienced a central nervous system embolic event for at least the first two weeks of antibiotic therapy. This time should allow for thrombus organisation and prevent the acute haemorrhagic transformation of embolic lesions. Reintroduction of anticoagulation in these patients should be done with caution, and prothrombin times should be monitored carefully (Salem et al., 2001).

In a follow-up to experimental data that demonstrated a salutary effect of intravenous aspirin therapy in established experimental *S aureus* endocarditis, a randomised trial in Canada compared oral aspirin 325 mg/d with placebo in 115 endocarditis patients (Kupferwasser et al.,1999). No compelling benefit was observed in aspirin-treated patients in terms of vegetation resolution and embolic events. Moreover, there was a trend toward more bleeding episodes in the aspirin-treated patients. Aspirin levels, a critical correlate of antimicrobial efficacy, were not monitored in this study (Kupferwasser et al., 1999).

2.2.4 INTRAOPERATIVE ECHOCARDIOGRAPHY

The use of aortic prosthesis/bioprosthesis is facilitated by preoperative estimates of annular size, which allow the selection of appropriately sized donor tissues. Intraoperatively, echocardiographic goals include assessment of not only the obviously dysfunctional valve but also the other valves and contiguous structures (Shapira et al., 2007).

Post-cardiopulmonary bypass images should confirm the adequacy of the repair or replacement and document the successful closure of fistulous tracts. Perivalvular leaks related to technical factors should be recognised and documented to avoid later confusion about whether the leaks are the results of recurrent infection. Afterload augmentation, however, may not mimic actual awake physiology and may still occasionally lead to an inaccurate evaluation of the awake postoperative state (Baddour et al., 2005).

During post-pump imaging, it is often necessary to augment afterload to reach representative ambulatory levels to avoid underestimation of regurgitant jet size and significance and to ensure that abnormal communications have been closed. Intraoperative TEE is mandatory in patients operated on for IE; it provides the surgeon with a final anatomical evaluation of valvular and perivalvular damage, and is particularly useful for assessing the immediate result of conservative surgery, as well as in cases of complex perivalvular repair (Shapira et al., 2007).

Finally, echocardiography must be used for follow-up of patients with IE under antibiotic therapy and after surgery, along with clinical follow-up. The number, type and timing of repeat examinations depend on clinical presentation, type of micro-organism and initial echocardiographic findings. After hospital discharge, the main complications include recurrence of infection, heart failure, need for valve surgery and death. Thus, clinical and echocardiographic periodic close follow-up (at one, three, six and 12 months) is mandatory during the first year after the end of antibiotic treatment (Habib et al., 2009).

2.2.5 ECHOCARDIOGRAPHY AT COMPLETION OF THERAPY

All patients who have experienced an episode of endocarditis remain at high risk of recurrent infection indefinitely. It is extremely important for the future care of these patients to establish a new baseline for valvular morphology, including the presence

of vegetations, ventricular function and valvular insufficiency once treatment has been completed (Habib et al., 2009).

Documentation of heart rate, heart rhythm and blood pressure at the time of the echocardiographic study is important because changes in these conditions may explain future differences in valvular insufficiency independent of pathology. Transthoracic Echocardiography is preferable for this because measurements of vegetation size are more reproducible and spectral Doppler interrogation is often more thorough than TEE (Habib et al., 2009).

Although intraoperative post-pump TEE views may be adequate for this new baseline, they should be reviewed for adequacy and repeated if nessecary. Some patients will have valvular dysfunction at the end of otherwise successful treatment; clearly, they will eventually require surgery. Post-treatment echocardiography can guide both medical management and the discussion of the appropriate timing of the intervention (Habib et al., 2009).

CHAPTER THREE: METHODS

The aim of the study was to correlate the echocardiographic findings with the intra-operative findings of patients with IE at Dr George Mukhari Hospital (DGMH). The objectives of the study were as follows:

1. The principle objective was to compare the echocardiographic findings with intraoperative and histological findings.

2. The second objective was to assess the outcome of patients with infective endocarditis at DGMH.

3. The third objective was to assess the severity of complications in patients with infective endocarditis at DGMH.

4. The fourth objective was to compare blood cultures of positive IE to echocardiographic findings.

5. The final objective was to assess the effect of IE on the left ventricular function.

The study design was a prospective, quantitative and observational study of 40 patients with IE at DGMH. The patient number recruited for the study was verified by the biostatistician from the University of Limpopo (Medunsa Campus) and was sufficient to show statistical significance. The plan of the entire research process was set up as indicated in Appendix A and B.

The Duke criteria were used for diagnosis of IE (Li et al., 2000). They are based on the following major and minor criteria:

Major criteria

1. Positive blood cultures for IE.

A. Typical micro-organisms consistent with IE from two separate blood cultures, as noted below:

- *Streptococci viridans, Streptococcus bovis, Staphylococcus aureus*; or

- Community acquired enterococci, in the absence of a primary focus;

or

B. Micro-organisms consistent with IE from persistently positive blood cultures defined as:

- two or more positive cultures of blood samples drawn >12 hours apart

- all of three or a majority of four or more separate cultures of blood (with first and last sample drawn >1 hour apart)

2. Evidence of endocardial involvement

A. Echocardiogram positive for IE

Vegetation

Abscess

New partial dehiscence of prosthetic valve

B. New valvular regurgitation (worsening or changing of pre-existing murmur is not sufficient)

Minor criteria:

Predisposition: predisposing heart condition, injection drug use

Fever: temperature >38^0C

Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhages, Janeway's lesions

Immunologic phenomena: glomerulonephritis, Olser's nodes, Roth's spots, rheumatoid factor positive

Microbiological evidence: positive blood culture but does not meet a major criterion (Sexton et al., 2000).

3.1 SELECTION CRITERIA

Patients enrolled in the study were required to meet the following inclusion criteria:

Inclusion criteria

1. All patients with IE in the aortic, mitral or tricuspid valve requiring surgical intervention.

2. Adult patients ranging from 20-45 years.

3. All patients who signed informed consent forms.

The following patients were excluded from the study: Signed informed consent

Exclusion criteria

1. Cardiac patients who had congenital heart diseases (e.g. ventricular septal defects, patent ductus arterioses, atrial septal defects).

2. Critically ill or unstable patients with IE.

3. Patients with IE of non-bacterial origin (e.g myxoma, viral and fungal).

Before commencement of the actual investigation, ethical approval was obtained from the Durban University of Technology Ethics Committee and permission was also obtained from DGMH and the Department of Health (Appendix D and E). In order to facilitate the study, the research plan was presented to the Departments of Cardiothoracic Surgery, Cardiology, Internal Medicine, Cardiac Clinical Technologist and cardiac nursing staff at DGMH.

Patients who met the inclusion criteria were recruited in the cardiac clinic. A letter of information and a consent form, drawn up by the researcher in both English and Setswana, was presented to all patients participating in the study. Patients were

notified as to the purpose and the requirements of the study. Patients were informed that participation in the research was entirely voluntary and that they were entitled to withdraw at any point without affecting the medical treatment rendered to them. They were also informed that all information used in the investigation would remain confidential and that any data reported in scientific journals or published would not include information identifying them as a patient in the study (refer to appendix F for consent in English and Setswana). All patients recruited to take part in the study were under the care of the consultant Head of Department of Cardiology who confirmed that the patients had IE.

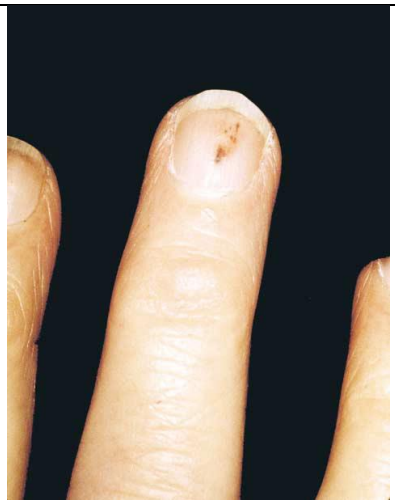
Patients who were willing to participate signed the consent form and were randomised. The challenges associated with the data collection were the following:

1. Forty (40) patients were randomised. Some cases did not qualify because the age of the participant exceeded the age group. The patient's age group was clearly and repeatedly specified verbally and in writing before and during the study.
2. Some patients with IE died before the operation, so the researcher was not able to get enough data.
3. Some patients died during the operation, so insufficient data were collected.

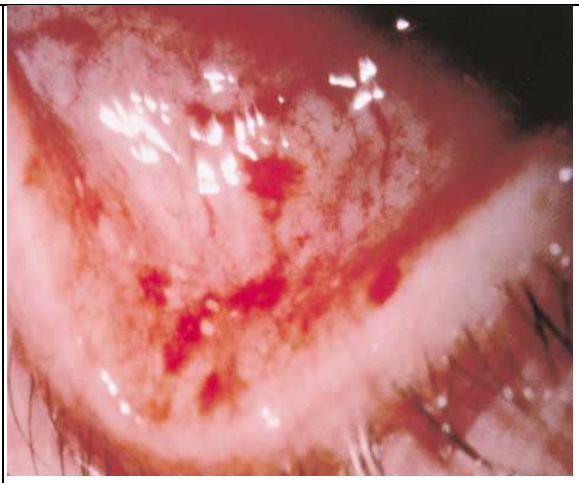
3.2 SEQUENCE OF DATA COLLECTION

Step 1. Patient identification:

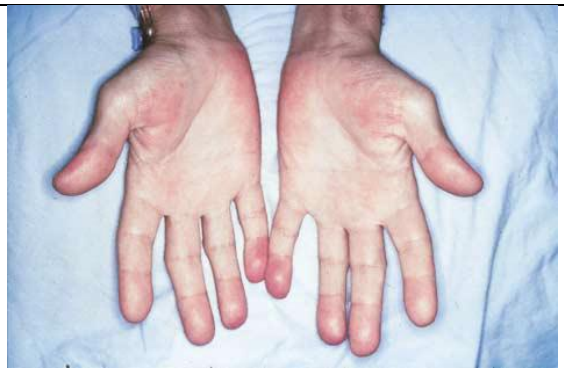
Patients were identified through the referral system and incidentally by echocardiography. A cardiologist/physician examined the patients clinically for features of IE (Figures 12 and 20). These features included splinter haemorrhages, conjunctival petechiae, Osler's nodes and Janeway's lesions, which are illustrated in Figure 12.



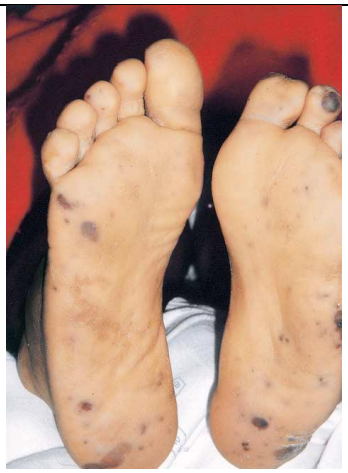
Splinter haemorrhages are normally seen under the fingernails or toenails. They are usually linear and red for the first two to three days and brownish thereafter.



Conjunctival petechiae.



Osler's nodes are tender, subcutaneous nodules, often in the pulp of the digits or the then areminence.



Janeway's lesions are nontender erythematous, hemorrhagic, or pustular lesions, often on the palms or soles.

Figure 12: Common peripheral manifestations of infective endocarditis (Mylonakius et al., 2001).

Step 2. Incidental finding: Finding of IE on the basis of an echocardiogram, symptoms and signs of IE.

An echocardiogram was performed by the team of echocardiographers to assess which valve was affected using the Aloka echocardiogram machine (Figure 13), the aloka adult probe (Figure 15) and Aquasonic ultrasound gel (Figure 14). Measurements of the ejection fraction, the size of the left ventricle and the size of the vegetation/mass or abscess were taken.The two views that were used were the parasternal and long-axis views (Figures 16 to 17).

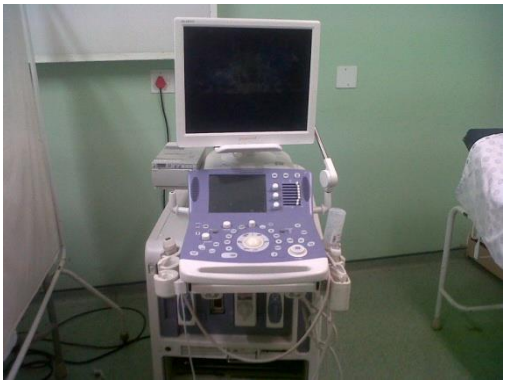


Figure 13: The 2D echocardiogram machine used to perform echocardiography.

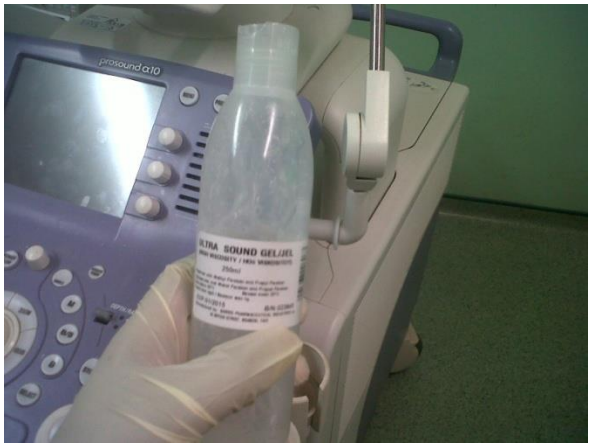


Figure 14: The ultrasound gel used on the patients when performing an echocardiography.

Figure 15: The adult probe used on all patients in Cardiology at DGMH with IE.

The parasternal long axis view that was used on the patient with endocarditis was as follows (Figure 16).

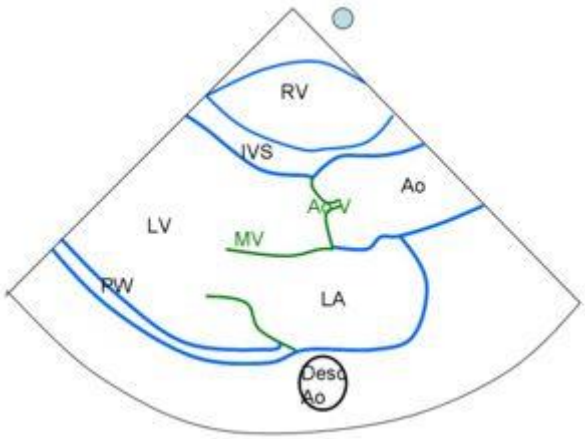


Figure 16: Parasternal long-axis view was used on the patient with infective endocarditis.

Procedure for obtaining the parasternal long axis

The parasternal window is located next to the sternum, between the 3rd and 4th intercostal spaces. The following steps were followed by the researcher:

The notch on the probe was directed toward the sternum, at 9-10 o'clock. The probe was placed against the left lateral border of the sternum, just at the sterno-costal angle. In order to set a good image the researcher started at the highest intercostals space (3rd or 4th), if the image was not good the researcher went to the next lower intercostals space. -Rv: The right ventricle was on top, closer to the probe. In this view the researcher saw the right ventricle outflow tract. Then looked for a right ventricle dilatation (diameter >⅔ the diameter of the left ventricle). Then got an idea of the right ventricular contractility. -Lv: Measurement of the size and wall thickness. -AoV: Aortic valve: Looked at the opening of the aortic cusps. With colour Doppler the researcher looked for aortic regurgitation. -IVS: Interventricular septum and PW: posterior wall. Thickness and contractility was assessed. -Ao: Aortic root. The aortic root should be parallel. -LA: Left atrium. It had the same diameter as the aortic root. -Decs Ao: Descending aorta. It helped to distinguish between a pericardial and a left pleural effusion. -Pericardium: It is the most echoic structure, appearing very bright. This is the best view to distinguish between pericardiac and pleural effusions.

The procedure for four chamber view that was used as follows:

The probe was placed at the apex of the LV, located at the apical impulse. The probe was oriented toward the right shoulder, the notch at 2 or 3 o'clock.

The four chambers of the heart (left ventricle, left atrium, right ventricle and right atrium) was visualised, as well as the atrioventricular valves: mitral and tricuspid valves. The intersection between the four chambers drew a cross with the vertical line represented by interventricular and interatrial septa. The horizontal line was created by the alignment of the tricuspid and mitral valve. -RV: Right ventricle (Figure 17).

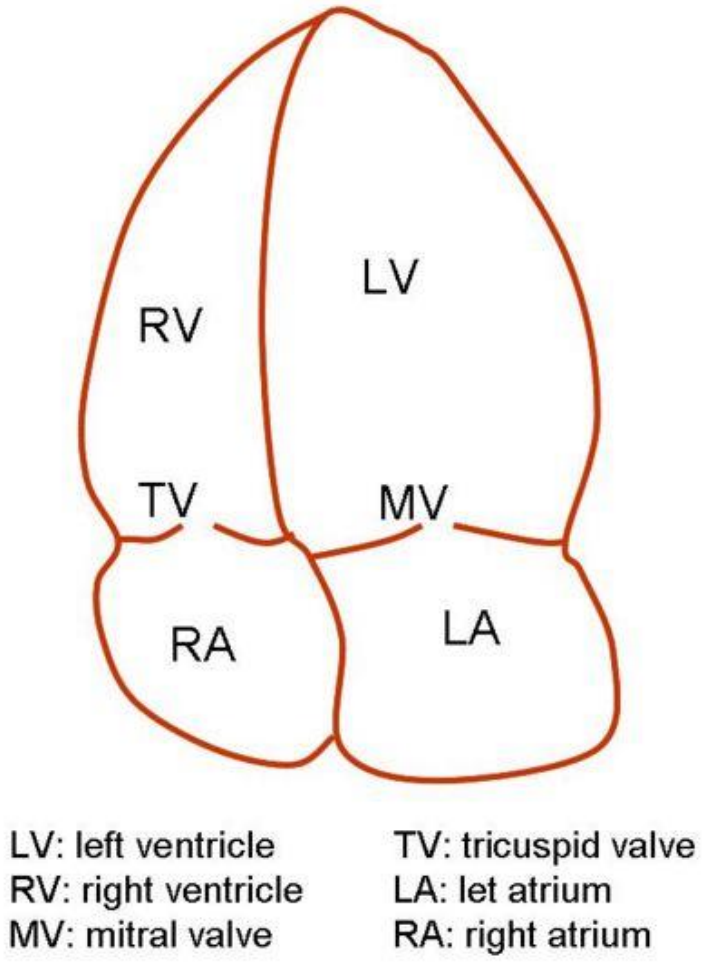
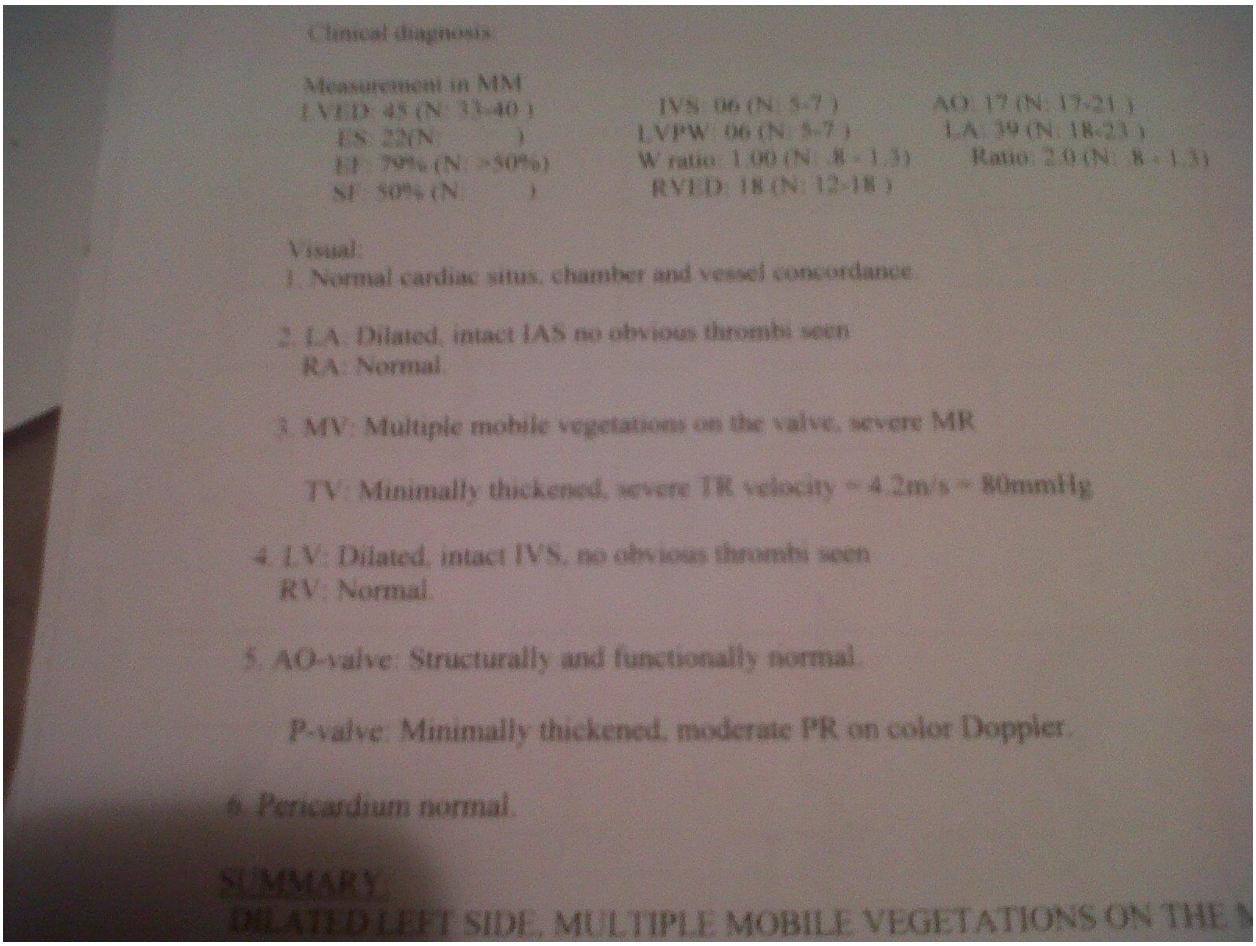


Figure 17: Four-chamber view was used on patients with infective endocarditis.

In apical four-chamber view, the RV was not larger than ⅔ of the LV width. The RV function was estimated by looking at the vertical motion of the lateral tricuspid annulus. The contraction of the RV was mainly longitudinal. -RA: Right atrium. -TV: Tricuspid valve. -LV: Left ventricle. The researcher assessed the overall function of the left ventricle and the contractility of the interventricular septum, apex and lateral wall. -LA: Left atrium. In this view the researcher measured the long and short axis of the LA and its area and volume. Most of the time the researcher saw that the merging of the pulmonary veins in the LA. -MV: Mitral valve. The anterior leaflet was close to the interatrial septum, the posterior leaflet was lateral. Apical four-chamber was a good view to assess the direction of a regurgitant jet and to quantitate mitral stenosis (with CW Doppler).

Step 3. Echocardiogram reports for patients with infective endocarditis on the mitral valve and severe mitral regurgitation. Measurements of the LVED, LVES, EF, SF were carried out. All the heart chambers were measured (Figure 18).


Clinical diagnosis:

Measurement in MM

LVED: 45 (N: 33-40)
ES: 22(N:)
EF: 79% (N: >50%)
SF: 50% (N:)

IVS: 06 (N: 5-7)
LVPW: 06 (N: 5-7)
W ratio: 1.00 (N: .8 - 1.3)
RVED: 18 (N: 12-18)

AO: 17 (N: 17-21)
LA: 39 (N: 18-23)
Ratio: 2.0 (N: .8 - 1.3)

Visual:

1. Normal cardiac situs, chamber and vessel concordance.

2. LA: Dilated, intact IAS no obvious thrombi seen
RA: Normal.

3. MV: Multiple mobile vegetations on the valve, severe MR.

TV: Minimally thickened, severe TR velocity = 4.2m/s = 80mmHg

4. LV: Dilated, intact IVS, no obvious thrombi seen
RV: Normal.

5. AO-valve: Structurally and functionally normal.

P-valve: Minimally thickened, moderate PR on color Doppler.

6. Pericardium normal.

SUMMARY:
DILATED LEFT SIDE, MULTIPLE MOBILE VEGETATIONS ON THE M

Figure 18: Echocardiographical measurements that were carried out at DGMH.

Step 4.The data recording for echocardiogram findings, clinical diagnosis before the operation and intraoperative findings (visual and histology) for patients with IE (Figure 19).

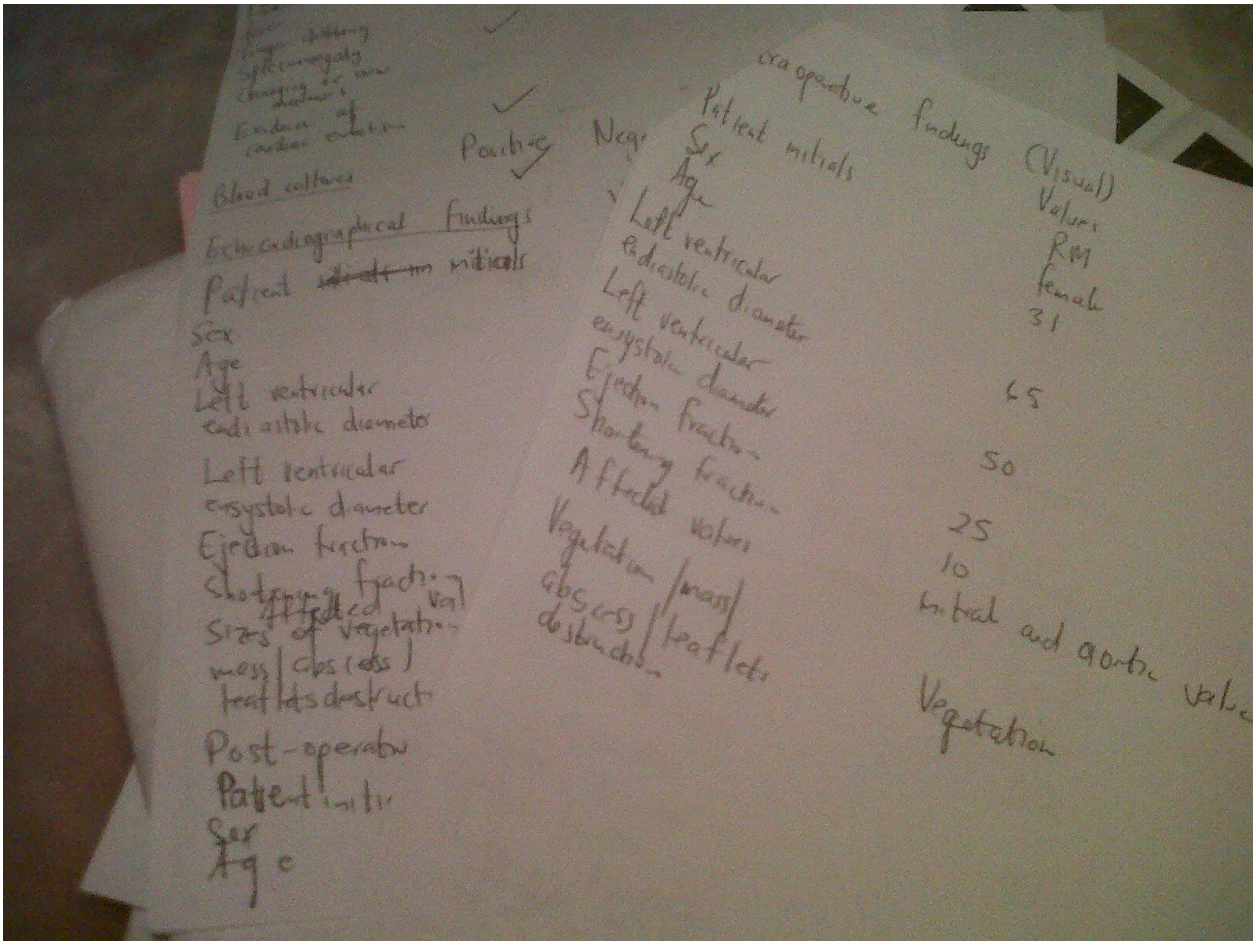


Figure 19: Data recording for echocardiographical findings and intraoperative findings.

Step 5. Blood was sent to the National Health Laboratory service in Pretoria, Medunsa SANAS (South African National Accreditation System) for culture in order to detect the presence of micro-organisms (Figure 20).

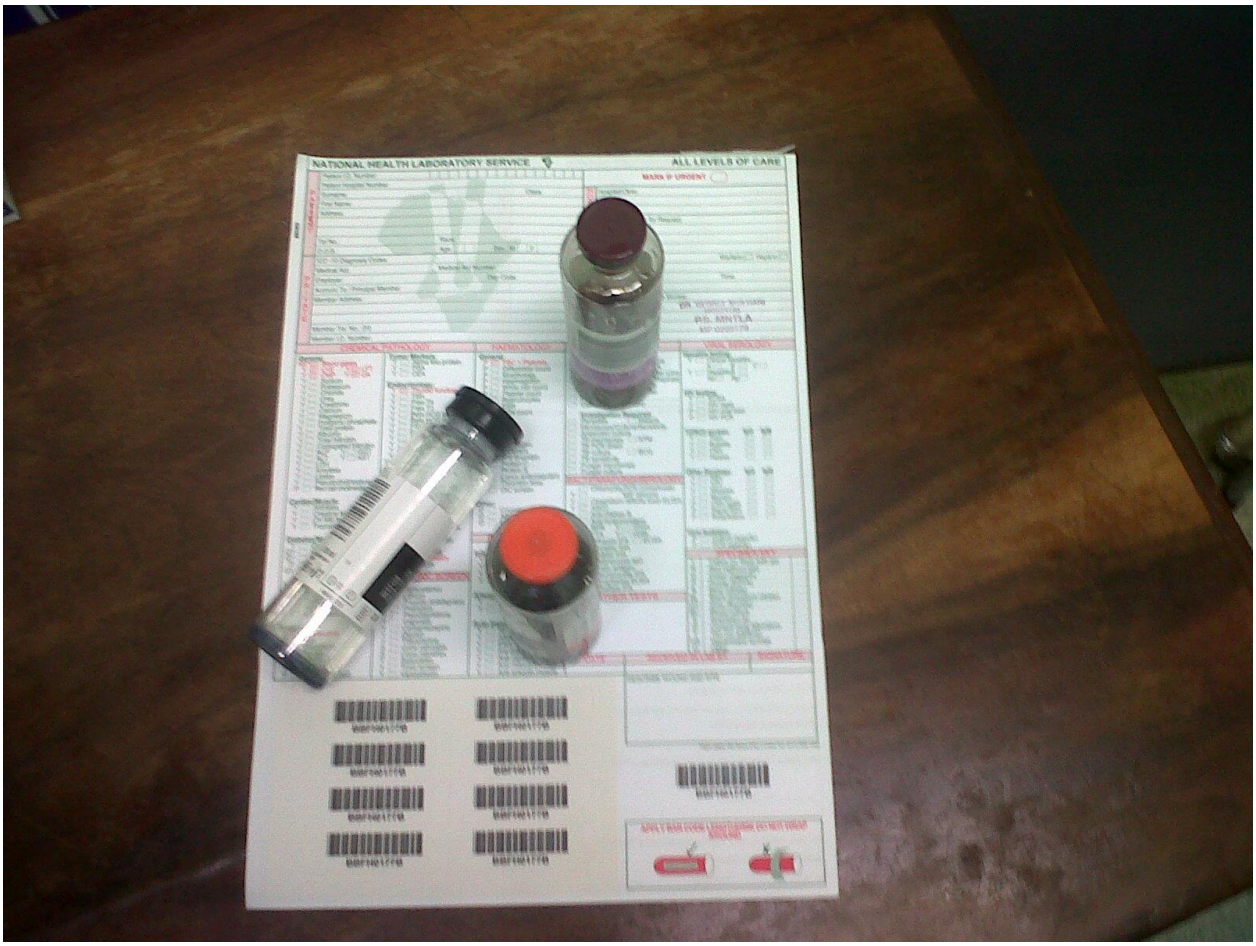


Figure 20: Blood collected and ready to be sent to the laboratory for Analysis.

If endocarditis was suspected, three sets of blood cultures (20 ml each; aerobic and anaerobic) was obtained within 24 hours; if presentation suggested ABE, cultures were prepared within the first one to two hours. If endocarditis was present and no prior antibiotic therapy was given, all three blood cultures are usually positive because the bacteraemia is continuous. At least one set of cultures is positive in 99% of cases. The use of empiric antibiotics was avoided in patients with acquired or congenital valvular or shunt lesions to avoid culture-negative endocarditis.

Step 6. For patients requiring heart surgery the cardiac surgeon performed the valve replacement, and the intra-operative findings were assessed visually and by using the TEE by the team of cardiologist and anaesthetist to confirm the presence of vegetation or abscess and leaflet destruction, as well as to look at the ventricular function and the size of ventricles. During the operation, which was performed by the team of cardiac surgeons, a biopsy sample was taken for histological examination to confirm the presence of vegetation or abscess. Thereafter, the cardiac surgeon performed the valve repair/replacement.

Step 7.The researcher had no access to the findings in the theatre, as the researcher was not present in the theatre. The results from the laboratory were then sent to the researcher. The researcher was then able to confirm if the presence of vegetation or mass/abscess and leaf destruction had been confirmed.

3.3 STATISTICAL ANALYSIS

SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA) was used for analysis of data. A p value of <0.05 is considered as statistically significant. Clinical data were compared between the intervention and control groups using Mann-Whitney tests for non-parametrically distributed dependent variables, t-tests for those which were normally distributed, and Pearson's chi square tests for categorical variables.

CHAPTER FOUR: RESULTS

4.1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Forty (40) participants were enrolled in the study. Their mean age ± standard deviation for echocardiography and intraoperative was 31.7±7.6 years and their ages ranged from 20 to 45 years. The descriptive statistics for age are shown in Table 4. No significant statistical difference was observed between echocardiograph and intraoperative for LVED (p>0.05).This was confirmed by a moderate correlation /association of (r=0.82) (Table 4).

Table 4: Comparative analysis of variables (AGE, LVED, LVES, EF and SF) of Echocardiography and Intraoperative.

Variables	Echocardiography		Intraoperative		P value	R value
	Mean± SD	Range	Mean ± SD	Range		
Age	31.2± 7.61	20-45	31.73 ± 7.61	20-45	P>0.05	r=1.0
LVED	53.8 ±8.65	38-80	53.43±10.24	39-70	P>0.05	r=0.819
LVES	34.97±8.58	19-59	34.12±9.62	19-50	P>0.05	r=0.677
EF	59.54±11.59	21-78	60.56±15.67	19-78	P>0.05	r=0.876
SF	31.36±7.14	10-45	32.8±10.11	8-45	P>0.05	r=0.798

No significant statistical difference was observed between echocardiograph and intraoperative measurements for LVED (p>0.05; r=0.82); between echocardiography and intraoperative data for LVES (p>0.05; r=0.68); between echocardiography and intraoperative data for EF (p>0.05; r=0.88) and between echocardiography and intraoperative data for SF (p>0.05; r=0.80) (Table 4).

There were nineteen of 25 (76%) male patients with IE on the mitral valve and aortic valve. There were ten of 15 (66%) female patients with IE on the mitral valve and aortic valve. There were six of 25 (24%) male patients with IE on the tricuspid valve. There were five of 15 (33%) female patients with IE on the tricuspid valve (Figure 21).

Twenty-five of the 40 (61%) were males and fifteen of 40 (39%) were females (Figure 22).

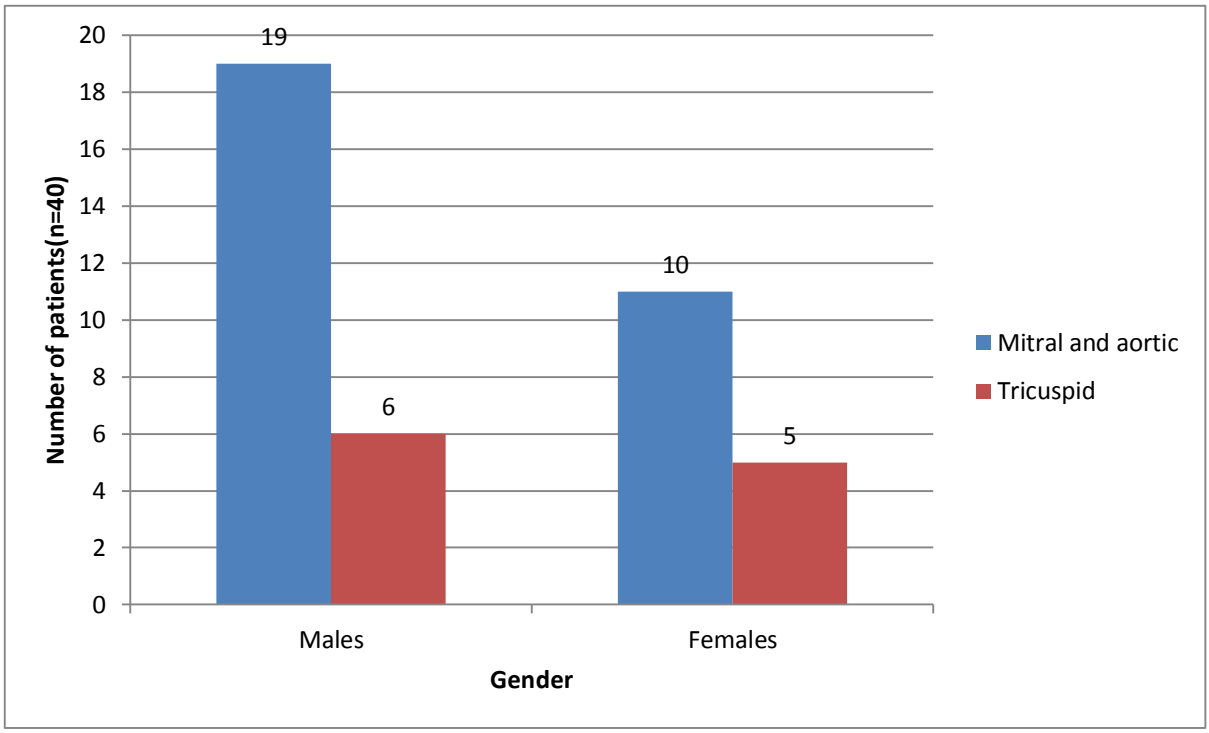


Figure 21: Gender distribution of patients with IE.

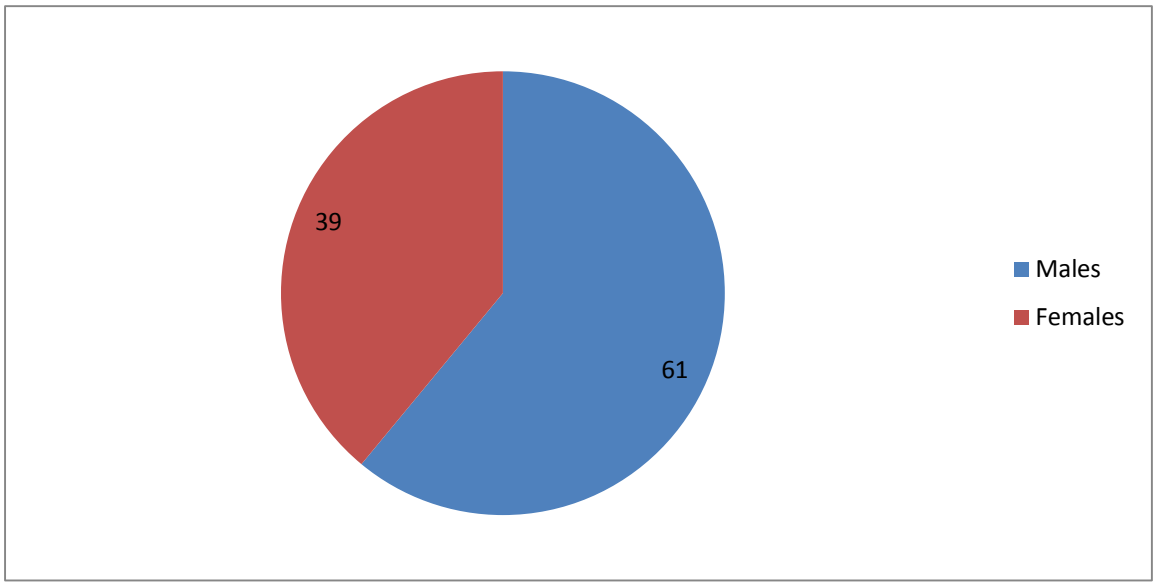


Figure 22: Gender distribution of patients with IE.

4.2 COMPARISON OF LVED OF ECHOCARDIOGRAPHY AND INTRAOPERATIVE FINDING

No significant statistical difference was observed between echocardiograph and intraoperative for LVED (p>0.05). This was confirmed by a graph below moderate correlation/association of (r=0.82) (Figure 23).

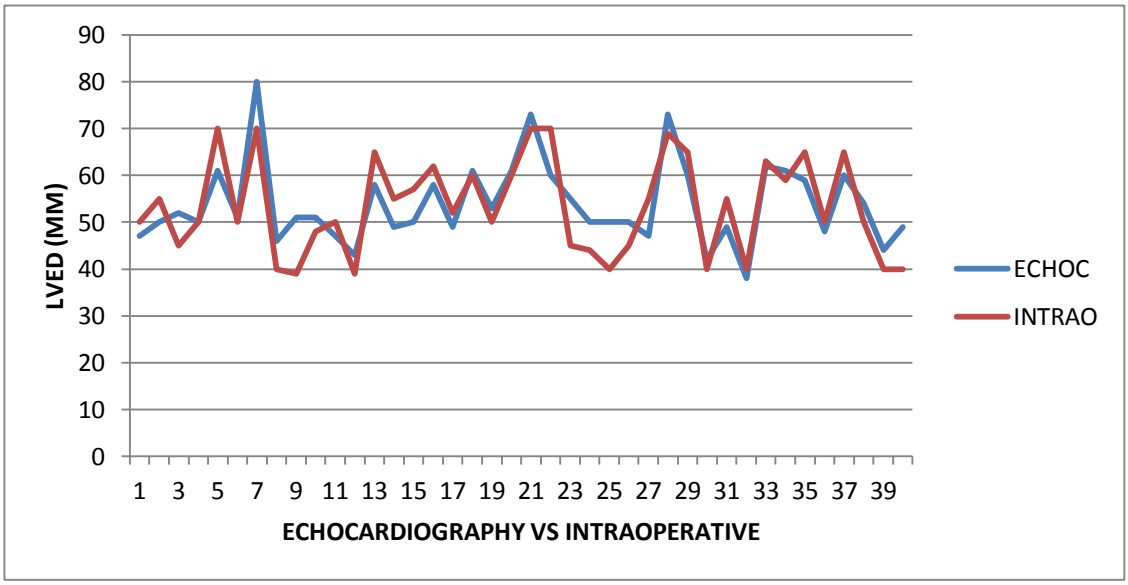


Figure 23: LVED of the echocardiography versus intraoperative.

The clinical diagnosis of all the patients (n=40) are represented in Table 5.

Clinical diagnosis	Percentages (%)	Number of patients
Anaemia	40%	16
Fever	90%	36
Finger clubbing	40%	16
Splenomegaly	40%	16
Changing or new murmurs	85%	34
Evidence of cardiac embolism	40%	16

Table 5: Clinical diagnosis.

Thirty two of 40 (80%) were culture positive and four of 40 (20%) culture negative. Preoperative findings included twenty four of 40 (60%) streptococci, eight of 40 (20%) enteroccoci, six of 40 (15%) mixture of organisms and two of 40 (5%) Gram negative bacilli. In eight of 40 (20%) a single valve was affected, twenty eight of 40 (70%) double valves were affected and four of 40 (10%) triple valves were affected.

The intraoperative and echocardiography findings showed thirty two of 40 (80%) vegetation, two of 40 (5%) perforation, four of 40 (10%) pseudo-aneursym and two of 40 (5%) abscesses. The prognosis of patients with poor ejection fraction (40-50% EF) was poorer than those with good ejection fraction (60-75%). The clinical findings of all patients confirmed infective endocarditis and thirty two of 40 (80%) blood cultures were positive and eight of 40 (20%) were negative. There were seven of 40 (17,5%) patients who showed poor correlation 40-50% between echocardiographical findings and post-operative findings. The results of thirty three of 40 (82%) patients showed perfect correlation 69% between the echocardiographical findings and post-operative findings. It detected eight of 40 (20%) had stenosis and thirty two of 40 (80%) had regurgitation in patients who had infective endocarditis.

CHAPTER FIVE: DISCUSSION

Infective Endocarditis has an estimated annual incidence of three to nine cases per 100,000 persons in industrialised countries (Durack et al., 1994). The male: female case ratio is more than 2:1 (Durack et al., 1994). The highest rates are observed among patients with prosthetic valves, intracardiac devices, unrepaired cyanotic congenital heart diseases, or a history of IE, although 50% of cases of IE develop in patients with no known history of valve disease (Durack et al., 1994). Other risk factors include chronic rheumatic heart disease (which now accounts for <10% of cases in industrialised countries), degenerative valvular lesions, haemodialysis, and coexisting conditions such as diabetes, human immunodeficiency virus infection and intravenous drug use (Andrews et al., 2001).

In the present study twenty-five of 40 patients (61 %) were males and fifteen of 40 patients (39%) were females carried results of the study indicates that the IE occurred at the Age range from 20-45, $p > 0.05$, $r=1.0$ (Table 4). More than one third of the cases of IE in the United States in were reported to be health care-associated (nosocomial or non-nosocomial) (Durack et al., 1994). The clustering of several of these predisposing factors with age probably explains the increased incidence of IE among persons 65 years of age or older (Durack et al., 1994).This may provide clinicians with the vital information to assist in reducing the death rate of patients.

The study found that 40% of patients with splenomegaly were well for more than six months. Within the clinical findings 90% of patients (n=36,n=34) had fever and 85% had changing or new murmurs (Table 5). Thirty two of 40 patients (80%) were culture positive and four of 40 patients (20%) were culture negative. Positive blood cultures are a major diagnostic criterion for IE and key to identifying the etiologic agent and the optimal antimicrobial regimen (Andrews et al., 2001).In a previous study wherever splenomegaly was reported in about 20% of cases. It was more in patients who had been ill for months rather than days or weeks (Werner et al., 1967).

Continuous bacteraemia and a high frequency of positive blood cultures are typical of this infection. In a study of 206 patients with blood cultures showing positive endocarditis, 95% of 789 blood cultures yielded the causative micro-organism, and in 91% of cases, all of the cultures were positive (Werner et al., 1967). The intensity of bacteraemia may not be great, however; <50 colony-forming units per millilitre of blood were detected in the majority of patients (Werner et al., 1967).

The Relative Survival Approach in Endocarditis: Even after the success of treatment, the patients who experienced IE were still subject to late complication including recurrence, the need for late valve surgery, and death. These events justify close follow-up, but their incidences and predictors were not well defined. The series was the largest that addressed this issue in adults (Frederic et al., 2012). The crude survival rates that was reported were in accordance with the most large series of IE. Relative survival was an approach that can be useful in clinical studies where although many clinical data are available it remains difficult to impute death to a specific disease. Moreover most recurrences and cardiac operations occurred during this crucial period (Frederic et al., 2012).

Acranobacterium haemolytic was first isolated from pharyngitis and skin infections in American soldiers and native islander in the South Pacific. The organism was often overlooked as part of the normal oral flora. No risk factor for infection have yet been identified although two distinct patient subsets are recognized: health young adults presenting with upper respiratory tract infections and older after immune compromised patients presenting with skin and soft tissue infections (Skov et al., 1998).

Current international guidelines advocate three parenteral treatment schedules for Endocarditis caused by viridans Streptococci which is highly susceptible to penicillin. The total daily dosage of penicillin varies from 12 to 18 million. High-dose antibiotics as recommended have a predominatly pharmacokinetic and pharmacodynamics rationale that is based mostly on experimental animal studies (Cremieux et al.,1991).

Timing of surgery requires experienced clinical judgement. Surgery is frequently required for abscess formation or persistent infection despite proper antimicrobial therapy or severe valvular regurgitation and intractable heart failure (Fuster et al., 2009). If heart failure caused by a correctable lesion is worsening, surgery may be required after only 24 to 72 hours of antimicrobial therapy (Fuster et al., 2009). In patients with prosthetic valves, surgery may be required when TEE shows valve dehiscence or a paravalvular abcess, when valve dysfunction precipitates heart failure, when recurrent emboli are detected or when the infection is caused by an antimicrobial-resistant organism (Fuster et al., 2009).

The findings of the present study suggest that at DGMH patients had IE on the left side of the heart (aortic and mitral valve) and right side of the heart (tricuspid valve). It also confirmed that there were 29 patients who had IE on the left side and 11 had on the right side (Figure 21). It also occurred in patients of all ages ranging from 20 to 45 years. Male: female ratio was 3:2 (Figure 22). According to Sexton et al. (2000), intravenous drug abusers and immune-compromised patients are at high risk and Infective Endocarditis occurs most often on the left side of the heart (e.g., mitral or aortic valve). They found that only 10-20% of cases are right-sided (tricuspid or pulmonic valve) and that Intravenous (IV) drug abusers have a much higher incidence of right-sided endocarditis (about 30-70%) (Sexton et al., 2000).

Acute bacterial endocarditis usually develops abruptly and progresses rapidly (Sternberg, 2004). A source of infection or portal of entry is often evident (Sternberg, 2004). When bacteria are virulent or bacterial exposure is massive, ABE can affect normal valves (Sternberg, 2004). It is usually caused *by S. aureus, group A haemolytic Streptococci, Pneumococci or Gonococci* (Sternberg, 2004). Prosthetic valvular endocarditis (PVE) develops in 2-3% of patients within one year after valve replacement and in 0.5%/yr thereafter (Vikram et al., 2003). It is more common after aortic than after mitral valve replacement and affects mechanical and bioprosthetic valves equally (Sternberg, 2004).

Many studies in the past, prior to 2003 have demonstrated that among the complications of IE, CHF has the greatest impact on prognosis (Vikram et al., 2003). Moderate to severe CHF was identified as one of five baseline features that were independently associated with six-month mortality in an investigation to validate a prognostic classification system for adults with complicated left-sided native valve IE (Vikram et al., 2003). In native valve IE acute CHF occurs more frequently in aortic valve infections (29%) than in mitral (20%) or tricuspid disease (8%) (Moon et al., 1997).

Mitral vegetations of any size are associated with a higher risk of embolisation (25%) than aortic vegetations (10%) (Konstadt et al., 1994).The highest embolic risk (37%) has been seen in the subset of patients with mitral vegetations attached to the anterior rather than the posterior mitral leaflet (Konstadt et al., 1994). In the present study the intraoperative and echocardiography findings showed presence of vegetation in 80% of the patients, the presence of perforation in 2% of patients, pseudo-aneurysm in 10% of patients and the presence of abscess in 8% of patients.

The effect of vegetation size on embolic potential was dependent on the infecting organism, with large vegetations independently predicting embolic events only in the setting of streptococcal IE (Vilacosta et al., 2002). In contrast, staphylococcal or fungal IE appears to carry a high incidence rate of embolisation independent of vegetation size (Vilacosta et al., 2002). In the present study, preoperative findings confirmed twenty four of 40 (60%) streptococci, eight of 40 (20%) enteroccoci, six of 40 (15%) mixture of organisms and two of 40 (5%) Gram negative bacilli. In eight of 40 (20%) single valve was affected, twenty eight of 40 (70%) double valves were affected and four of 40 (10%) triple valves were affected.

The role of echocardiography in predicting embolic events has been controversial (Heinle et al., 1994).Their study included four echocardiographers who were not granted access to clinical data, interobserver agreement was mixed on the characterisation of vegetations. Agreement was high for the presence of vegetation (98%) and site involved (97%); interobserver agreement was considerably less for vegetation size (73%), mobility (57%), shape (73%) and attachment (40%) (Heinle et al., 1994).

A 5 years old study confirmed a reduction in frequency of embolisation after two weeks of therapy (Mugge et al., 1989). Moreover, the latter study re-emphasised the increased risk of embolisation with increasing vegetation size during therapy, mitral valve involvement and staphylococcal causes. Prediction of individual patient risk for embolisation is extremely difficult. Many have attempted to use echocardiography to identify a high-risk subset of IE patients who might benefit from early surgery to avoid embolization (Mugge et al., 1989).

Echocardiographic evaluation of IE patients delineates the causes and severity of CHF. Ventricular size, wall motion and dynamic function can be readily defined and valve insufficiency quantified (Moon et al., 1997). Progressive chamber enlargement, elevation of pulmonary arterial pressures and increasing wall stress on serial evaluation all indicate a trend toward decompensation (Moon et., 1997). Medical and surgical treatment decisions can be guided by echocardiographic detection of fistulae, prosthetic dehiscence, obstructive vegetations, or flail leaflets (Moon et al., 1997).

Surgical approaches to IE patients with CHF must take into account the distortion of the valve and its surrounding structures. Severe valvular disruption will usually require prosthetic replacement (Mugge et al., 1989). Ruptured mitral chordate may sometimes be repaired with a combination of leaflet resection, chordal reattachment or transposition of an annular support. Leaflet perforations may be repaired with small pericardial patches if the surrounding leaflet tissue is well preserved and valve

motion can be maintained. Discrete vegetations on aortic or mitral leaflets have been excised along with underlying leaflet tissue and repaired with a patch (Mugge et al., 1989).

The outcome of surgery in the current study for active infective endocarditis in a cohort of patients during a three year interval, the probably reflect an accurate risk of surgery in patients with active infective endocarditis in a large tertiary care hospital. The indications for and timing of surgery were still controversial among interns who treated these patients, and the input of a cardiac surgeon was needed if mortality and morbidity were reduced. Close survelliance of these patients was indispensable to detect early failure of adequate antibiotic therapy to cardiogenic or septic shock and multi organ failure. It has been shown that cases of endocarditis caused by *S aureus* and other virulent microorganisms on valves in the left side of the heart were best treated with early surgery. The outcome of prosthetic valve endocarditis were worse than those of native valve endocarditis. It was found that not only was prosthetic valve endocarditis associated with higher operative mortality but it adversely affected long term survival relative to native valve endocarditis.

Echocardiography performed in the study showed a preserved left ventricular systolic function (EF>50%) in 80% of patients. In 20% left ventricular function was moderately depressed (EF between 35 and 50%). Overall moderate to severe valvular regurgitation occurred in 80% of patients with mitral and aortic involvement and 20% of patients with stenosis of both valves. The operative risk associated with multiple valve involvement did not exceed the risk of single valve disease, irrespective of the affected valve type and was accompanied by a significant increase in 90 day mortality (Kim et al., 2000).

Some authors have identified coinfection with human immunodeficiency virus (HIV) and a degree of immunosuppression as a risk factor of mortality in intravenous drug user (IVDU) patient with IE particularly in patients with cluster difference 4 (CD 4) cell counts <200/mm^3 (Cicalini et al., 2001).Two of patients were HIV infected. No

significant difference in the mortality rate according to the HIV infection serostatus were reported.This may have been attributable to the low number of affected patients (Cicalini et al., 2001).

Staphylococcus aureus was the most common pathogen isolated in the patient group but was not associated with significantly decreased 90 day survival when compared with other pathogens (Fowler et al., 2005). In contrast, other investigators have reported that *Staphylococcus aureus* associated IE was identified as the most common cause of IE and is an independent predictor of mortality (Fowler et al., 2005). For this reason therapy was changed in Staphylococcal IE to vancomycin and rifampicin if the preoperative antibiotic regime was ineffective post-operatively. Fowler et al study data showed that patients receiving concentrations $\geq$10mg/L vancomycin were more likely to become afebrile and most of them had a normal white blood cell count within 72 hours (Fowler et al., 2005).

Staphylococci are prone to cause abscess formation and early extracardiac organ manifestations. Fowler reported that infection with *Staphylococcus aureus* was associated with decreased survival compared to non-Staphylococcus aureus infection (Fowler et al., 2005). This suggests that surgical treatment should be performed earlier when patient is in less advanced state of systemic infection. In Fowler et al study two patients died 6 and 8 days after surgery, whereas one patient died after 591 days. The cause of death was severe sepsis in the first two cases and sudden death in the third. The patients who died before post-operative day 30 suffered from severe bacteremia caused by *Staphylococcus aureus* and was mechanicaly ventilated and inotrope dependent (Fowler et al., 2005).

In the current study there were no reoperations and no recurrent infection in spite of all patients being in the active phase of endocarditis. This demonstrates the success with the radical approach in this institution. It did result in the onset of complete atrioventricular block postoperatively in two patients necessitating pacemaker

implantation. The deleterious effects of radical surgery are offset by benefits associated with the effective removal of infected tissue.

LIMITATIONS OF STUDY

The limitations of the study were:

The study was restricted to 40 cardiac patients with IE at DGMH. It would have been better to have had a larger sample size.

The study was limited due to time constrains of the M-Tech level, and due to budget the study was limited to one hospital.

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

The results of the study showed that there was a moderate correlation between the echocardiographical findings and intra-operative findings (visual and histology) for LVES (r=0.68).The IE may occur in the mitral or aortic, pulmonic and tricuspid valve. There was no highly significant difference between the echocardiography and intraoperative data for LVED ($p>0.05$). The study also showed that there was a moderate correlation between the echocardiographical findings and post-operative findings. The histological examination confirmed that all the patients had IE. The prognosis of patients with poor ejection fraction (40-50% EF) was poorer than with those with good ejection fraction (60-75%).

It is extremely important for the future care of these patients to establish a new baseline for valvular morphology, including the presence of vegetations, ventricular function and valvular insufficiency once treatment has been completed. Documentation of heart rate, heart rhythm and blood pressure at the time of the echocardiographic study is important because changes in these conditions may explain future differences in valvular insufficiency independent of pathology.

A TTE is preferable for this because measurements of vegetation size are more reproducible and spectral Doppler interrogation is often more thorough than TEE. Although intraoperative post-pump TEE views may be adequate for this new baseline, they should be reviewed for adequacy and repeated if necessary. Some patients will have valvular dysfunction at the end of an otherwise successful treatment; clearly, they will eventually require surgery. Post-treatment echocardiography can guide both medical management and the discussion of the appropriate timing of the intervention.

Echocardiography should be performed in all cases of suspected IE. Whether TTE or TEE should be performed first depends on the clinical scenario. If the clinical

suspicion is relatively low or imaging is likely to be of good quality, then it is reasonable to perform TTE. When imaging is difficult or poor, TEE should be considered. If any circumstances that preclude securing optimal echocardiographic windows including chronic obstructive lung disease, previous thoracic surgery, morbid obesity, or other conditions, then TEE should be performed instead of TTE. If TTE is negative and clinical suspicion remains low, then other clinical entities should be considered.

If TEE shows vegetation but the likelihood of complications is low, then subsequent TEE is unlikely to alter initial medical management. On the other hand, if clinical suspicion of IE or its complications is high (prosthetic valve, staphylococcal bacteraemia, or new atrioventricular block), then negative TTE will not definitely rule out IE or its potential complications and TEE should be performed first.

Investigation in adults have shown TEE to be more sensitive than TTE for detection of vegetation and abscesses. In addition, in the setting of a prosthetic valve, transthoracic images are greatly hampered by the structural components of a prosthesis and are inadequate for assessment of the perivalvular area where those infections often start. Although cost-effectiveness calculations suggest that TEE should be the first examination in adults suspected of having IE, particularly in the setting of staphylococcal bacteraemia, many patients are not candidates for immediate TEE because of oral intake during the preceding six hours or because the patients are in institutions that cannot provide 24-hour TEE services (Reynolds et al., 2003).

Both TEE and TTE may produce false negative results if vegetations are small or have already embolised. Even TEE may initially miss a perivalvular abscess, particularly when the study is performed early in the patient's illness. In such cases, the incipient abscess may be seen only as a nonspecific perivalvular thickening, which on repeat imaging across several days may become recognisable as it expands and forms cavities. Similarly, perivalvular fistulae and pseudo-aneurysms

develop over time, and negative early TEE images do not exclude the potential for their development (Daniel et al., 1991).

A transoesophageal echocardiogram is more accurate but in this study it was found that TTE can be accurate if one compares it with intraoperative (visual and histology) results, even though the echocardiogram is operator-dependent. All patients with IE who come to DGMH may need urgent surgery to prevent complications and a fatal outcome. The cardiologist must examine the patient clinically for features of IE and must send the patients to the clinical technologist to perform an echocardiogram to confirm if there are vegetations/masses/abscesses, immediately perform the blood cultures so that the patients can have the surgery immediately to prevent complications. During surgery the cardiac surgeon will then decide whether to repair or replace the affected valve.

A negative echocardiogram may be observed in about 15% of cases of IE. The imaging diagnosis may be particularly challenging in some cases, such as those involving intracardiac devices, valvular prostheses, the presence of pre-existing severe lesions (mitral valve prolapse, degenerative lesions), very small vegetations and abscesses or no vegetation. In addition, the diagnosis may be difficult at the early stage of the disease. Conversely, false diagnosis of IE may occur in other situations: for example, it may be difficult to differentiate between vegetations and thrombi, cusp prolapse, cardiac tumours, myxomatous changes, Lambl's excrescences or strands. Thus, in some situations, the echocardiogram remains negative or doubtful, even if it is performed by expert hands and after a repeat examination (Hill et al., 2007).

Imaging of IE remains a diagnostic challenge because echocardiography has several limitations, which can have an impact on patient prognosis. Novel imaging modalities are emerging and offer hope of better management of the disease and thus a reduction in mortality. Some of these methods provide a better morphological

evaluation of the intra- and extracardiac damage; others allow visualisation of the inflammation and infection at the molecular level.

ADVANTAGES AND RECOMMENDATIONS OF STUDY

The use for specialists or generalists who are seeking the latest information on the treatment and management of IE is limited, but the study will still serve as a reference for specialists who seek a thorough historical review of a specific facet of the broad topic of IE.

The study will also be useful for residents in internal medicine or surgery and fellows in infectious diseases who want a comprehensive review of the clinical and pathological features of IE or a general overview of specific types of the disease.

Finally, blood cultures should be taken of patients with IE at DGMH, Department of Cardiology and depending on the results, an echocardiogram should be done to assess the chamber size, vegetation size and function of the heart. In order to prevent fatalities and complications, the patient should undergo cardiac surgery. The cardiac technologist should therefore play an active role in the measurements of echocardiogram and intraoperative data.

Further study will be undertaken to involve more hospitals in the province.

CHAPTER SEVEN: REFERENCES

Alsip, S.G., Blackstone, E.H., Kirklin, J.W., and Cobbs C.G., (1985). Indications for cardiac surgery in patients with active infective endocarditis*. Am J Medical,* **78**: 138–148

Andrews, M.M., and Von Reyn CF., (2001). Patient selection criteria and management guidelines for parenteral antibiotic therapy for native valve infective endocarditis. *Circulation*, **32**: 203-209

Baddour, L.M., Wilsom W.R., and Bayer A.S., (2005). Infective endocarditis: Diagnosis therapy, and management of complications. *Complications*, **111**: 394-434

Bayer, A.S., (1993). Infective endocarditis*. Clin Infect Dis*. **17**: 313–320

Bayer, A.S., Bolger, A.F., and Taubert K.A., (1998). Diagnosis and management of infective endocarditis and its complications. *Circulation*, **98**: 2936-48

Berlin, J.A., Abrutyn E., and Strom B.L., (1995). Incidence of infective endocarditis in the Delaware Valley, 1988-1990. *Am J Cardiol*, **76**: 933-6

Bingham, W.F., (1977).Treatment of mycotic intracranial aneurysms. *J Neurosur, **46**:* 428–437.

Bohmfalk, G.L., Story J.L., Wissinger J.P., and Brown WE Jr., (1978). Bacterial intracranial aneurysm. *J Neurosurg,* **48**: 369–382

Braunwald, E., (1996). Heart disease. A textbook of cardiovascular medicine. 5th ed. W Saunders

Brouqui, P., and Raoult, D., (2001). Endocarditis due to rare and fastidious bacteria. *Clin Microbiol Rev*, **14**:177-207

Brusch, J.L., (2007). Infective endocarditis and its mimics in the critical care unit. *Infectious Diseases in Critical Care*, **2**: 261-2

Cabell, C.H., Barsic, B., Bayer, A.S., Hoen, B., Olaison, L., Fowler, V.G J.r., Miro, J.M., Chen, A., Stafford, J., Gordon, D., Peterson, G., Spelman, D., Selton-Suty, C., Korman, T and Abrutyn, E., (2003). Clinical findings, complications, and outcomes in a large prospective study of definite endocarditis: The International Collaboration on Endocarditis—Prospective Cohort Study. Paper presented at 7th International Symposium on Modern Concepts in Endocarditis and Cardiovascular Infections

Cabell, C.H., Jollis, J.G., Peterson, G.E., Corey, G.R., Anderson, D.J., Sexton, D.J., Woods, C.W., Reller, L.B., Ryan, T., and Fowler, V.G Jr., (2002). Changing patient characteristics and the effect on mortality in endocarditis. *Arch Intern Med,* **162**: 90–94

Chan, K.L., Dumesnil, J.G., Cujec, B., Sanfilippo, A.J., Jue, J., Turek, M.A., Robinson, T.I., and Moher, D., (2003). Investigators of the Multicenter Aspirin Study in Infective Endocarditis. A randomized trial of aspirin on the risk of embolic events in patients with infective endocarditis. *J Am Coll Cardiol,* **42**: 775–780

Chapot, R., Houdart, E., Saint-Maurice, J.P., Aymard, A., Mounayer, C., Lot G., and Merland,J.J., (2002). Endovascular treatment of cerebral mycotic aneurysms. *Radiology,* **222**: 389–396

Chu, V.H., Cabell, C.H., Benjamin, D.K Jr., Kuniholm, E.F., Fowler, V.G Jr., Engemann, J., Sexton, D.J., Corey, G.R., and Wang, A., (2004). Early predictors of in-hospital death in infective endocarditis*. Circulation,* **109**: 1745–1749

Cicalini, S., Forcina, G., De Rosa, F.G. (2001). Infective endocarditis in patients with human immunodeficiency virus infection. *J Infect*, **42**: 267- 271

Covarrubias, E.A., Sheik, M.U., and Fox, L.M., (1977). Echocardiography and pulmonary embolism. *Echocardiography*, **87**: 720

Cremieux, A.X ., Maziere, B.,Vallois, J.M., (1991). Creftriaxone diffusion into cardiac fibrin vegetation. Qualitative and quantitative evaluation by autoradiography. *Fundam Clin Pharmacol,* **5**: 53-60

Daniel, W.G., Mugge, A., Martin, R.P., Lindert, O., Hausmann, D., Nonnast-Daniel, B., Laas, J., and Lichtlen, P.R., (1991). Improvement in the diagnosis of abscesses associated with endocarditis by transesophageal echocardiography*. N Engl J Med,* **324**:795–800

Dillon, J.C., (1973). Echocardiographic manifestations of valvular vegetations. *American Heart Journal*, **86**:69

Durack, D.T., Lukes, A.S and., Bright D.K., (1994). New criteria for diagnosis of infective endocarditis: Utilization of specific echocardiographic findings. *Heart*, **96**: 200-9

Erbel, R., Rohmann, S., Drexler, M., Mohr-Kahaly, S., Gerharz, C.D., Iversen, S., Oelert H., and Meyer, J., (1988). Improved diagnostic value of echocardiography in patients with infective endocarditis by transoesophageal approach: Aprospective study*. Eur Heart J,* **9**: 43–53

Evangelista, A., Gonzalez-Alujas, M.T., (2004). Echocardiography in infective endocarditis. *Heart*, **90**: 614—7

Fernandez-Guerrero, M.L., Verdejo, C., Azofra, J., and de Gorgolas, M., (1995). Hospital-acquired infective endocarditis not associated with cardiac surgery: Anemerging problem. *Clin Infect Dis*, **20**:16-23

Fowler, V.G., Miro, J.M., Hoen, B., Cabell, C.H., (2005). Staphylococcus aureus endocarditis: a consequence of medical progress. *J Am Med Assoc,* **293**: 3012-3021

Francioli, P., (1991). Central nervous system complications of infective endocarditis.In: Scheld WM, Whiteley RJ, Durack D,eds. *Infections of the Central Nervous System*. New York, NY*: Raven Press.*515–559

Frederic, C., Didier, R., Gilbert, H., (2012). The Relative survival approach in endocarditis. *Am Heart J,* **164**: 94-101

Fuster, V., and Walsh, R.A., (2009). Hurst's The Heart. 13th ed. New York: McGraw-Hill Education

Geraci, J.E., (1958). The antibiotic therapy of bacterial endocarditis: Therapeutic data on 172 patients seen from 1951 through 1957; additional observations on short-

term therapy (two weeks) for penicillin-sensitive streptococcal endocarditis. *Med Clin N Am,* **42**: 1101–1140

Goldenberger, D., Kunzl, A., Vogt, P., Zbinden, R., and Altwegg, M., (1997). Molecular diagnosis of bacterial endocarditis by broad-range PCR amplification and direct sequencing. *J Clin Microbiol,* **35**: 273-39

Habib, G., Hoen, B., Tornos, P., (2009). Guidelines on the prevention, diagnosis, and treatment of infective endocarditis: The Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. *Eur Heart J*, **30**: 2369-413

Habib, G., Badano, L., Tribouilloy, C., (2010). Recommendations for the practice of echocardiography in infective endocarditis. *Eur J Echocardiogr*, **11**: 202—19

Heinle, S., Wilderman, N., Harrison, J.K., Waugh, R., Bashore, T., Nicely, L.M., Durack, D., and Kisslo, J., (1994). Value of transthoracic echocardiography in predicting embolic events in active infective endocarditis. Duke Endocarditis Service. *Am J Cardiol,* **74**:799– 801

Hill, E.E., Herijgers, P., Claus, P., (2007). Abscess in infective endocarditis: The value of transesophageal echocardiography and outcome: A 5-year study. *Am Heart J*, **154**: 923—8

Hoen, B., Selton-Suty, C., and Lacassin, F., (1995). Infective endocarditis in patients with negative blood cultures: Analysis of 88 cases from a one-year nation wide survey in France. *Clin Infect Dis*, **20**: 501-6

Huston, J III., Nichols, D.A., Luetmer, P.H., Goodwin, J.T., Meyer, F.B., Wiebers, D.O., and Weaver, A.L., (1994). Blinded prospective evaluation of sensitivity of MR angiography to known intracranial aneurysms: Importance of aneurysm size. *Am J Neuroradiology,***15**: 1607–1614

Jackman, J.D Jr., and Glamann, D.B., (1991). Gonococcal endocarditis: Twenty-five year experience. *Am J Med Sci,* **301**: 221–230

Kang, D.H., Kim, Y.J., Kim, S.H., (2012). Early surgery versus conventional treatment for infective endocarditis. *N Engl J Med*, **366**: 2466-73

Kim, N., Lazzar, J.M., Cunha, B.A., Lia, W., Minnagati, V. (2000). Multi- valvular endocarditis. *Clin Microbiol*, **6**: 207- 212

Konstadt, S.N., Louie, E.K., Shore-Lesserson, L., Black, S., and Scanlon, P., (1994). The effects of loading changes on intraoperative Doppler assessment of mitral regurgitation. *Cardiothoracic Vacs Anesth,* **8**:19–23

Kupferwasser, L.I., Yeaman, M.R., Shapiro, S.M., Nast, C.C., Sullam, P.M., Filler, S.G., and Bayer, A.S., (1999). Acetylsalicylic acid reduces vegetation bacterial density, haematogenous bacterial dissemination, and frequency of embolic events in experimental Staphylococcus aureus endocarditis through antiplatelet and antibacterial effects. *Circulation***, 99**: 2791–2797

Li, J.S., Sexton, D.J., Mick, N., (2000). Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*, **30**: 633—8

Lind, D.A., Marchal, W.G., and Mason, R.D., (2004). Statistical Techniques in Business and Economics.11thed.New York: McGraw Hill

Liu, Y.W., Tsai, W.C., Lin, C.C., (2009). Usefulness of real-time three-dimensional echocardiography for diagnosis of infective endocarditis. *Scand Cardiovasc J,* **43**:318-23

Mandell, G.L., Kaye, D.D., Levison, M.E., and Hook, E.W., (1970). Enterococcal endocarditis: An analysis of 38 patients observed at the New York Hospital-Cornell Medical Center. *Arch Intern Med,* **125**: 258–264

Mansur, A.J., Grinberg, M., Leao, P.P., Chung, C.V., Stolf, N.A., and Pileggi, F., (1986). Extracranial mycotic aneurysms in infective endocarditis. *Clin Cardiol,* **9**: 65–72

Mathew, J., Addai, T., and Morrobel, A., (1995). Intravenous drug abuse. *Drug Abuse*, **15**:1641-8

Middlemost, S., Wisenbaugh, T., Meyerowitz, C., Teeger, S., Essop, R., Skoularigis, J., Cronje, S., and Sareli P., (1991). A case for early surgery in native left-sided endocarditis complicated by heart failure: Results in 203 patients. *Am Coll Cardiol,***18**: 663–667

Moon, M.R., Stinson, E.B., and Miller, D.C., (1997). Surgical treatment of endocarditis. *Prog Cardiovascular Dis,* **40**: 239–264

Moreillon, P., (2004). Infective Endocarditis. *Lancet*. **363**:139-47

Moskowitz, M.A., Rosenbaum, A.E., and Tyler, H.R., (1974). Angiographically monitored resolution of cerebral mycotic aneurysms. *Neurology,* **24**: 1103–1108

Mugge, A., Daniel, W.G., Frank, G., and Lichtlen P.R., (1989). Echocardiography in infective endocarditis: Reassessment of prognostic implications of vegetation size determined by the transthoracic and the transesophageal approach. *Am Coll Cardiol,* **14**: 631–638

Mylonakius, E., (2001). Infective endocarditis. *New Engl J Med*, **18**:1318-1319

Nguyen, M.H., Nguyen, M.L., Yu, V.L., McMahon, D., Keys, T.F., and Amidi, M., (1996). Candida prosthetic valve endocarditis: Prospective study of six cases and review of the literature. *Clin Infect Dis,* **22**: 262–267

Pazin, G.J., Saul, S., and Thompson, M.E., (1982). Blood culture positivity: suppression by outpatient antibiotic therapy in patients with bacterial endocarditis. *Arch Intern Med,* **142**: 263–268

Pierrotti, L.C., and Baddour, L.M., (2002). Fungal endocarditis. *Chest,* **122**: 302–310

Polit, D., and Beck, C., (2006). Essentials of nursing research –Methods, appraisals and utilization. 6th ed. Philadepia: Lippincott, Williams and Wilkins.

Reynolds, H.R., Jagen, M.A., Tunick, P.A., and Kronzon, I., (2003). Sensitivity of transthoracic versus transesophageal echocardiography for the detection of native valve vegetations in the modern era. *J Am Soc Echocardiogram,* **16**: 67–70

Rice, L.B., Calderwood, S.B., Eliopoulous, G.M., Farber, B.F., and Karchmer, A.W., (1991). Enterococcal endocarditis: A comparison of prosthetic and native valve disease. *Rev Infect Dis,* **13**:1–7

Robinson, S.L., Saxe, J.M., Lucas, C.E., Arbulu, A., Ledgerwood, A.M., and Lucas, W.F., (1992). Splenic abscess associated with endocarditis. *Surgery,* **112**: 781–786

Rohmann, S., Seifert, T., Erbel, R., Jakob, H., Mohr-Kahaly, S., Makowski, T., Gorge, G., Oelert, H., and Meyer, J., (1991). Identification of abscess formation in native-valve infective endocarditis using transesophageal echocardiography: Implications for surgical treatment. *Thorac Cardiovascular Surg,* **39**: 273–280

Salem, D.N., Daudelin, H.D., Levine, H.J., Pauker, S.G., Eckman, M.H., and Riff, J., (2001). Antithrombotic therapy in valvular heart disease. *Chest,* **119**: 207S–219S

Saunders, W.B., (2005). Robbins pathologic basis of disease. *Phatology***. 47**:131-32

Selton-Suty, C., Célard, M., and Le Moing, V., (2012). Pre eminence of Staphylococcus aureus in infective endocarditis: A 1-year population-based survey. *Clin Infect Dis*, **54**:1230-9

Sexton, D.J., and Mick, N., (2000). Clinical infectious diseases. *Infectious*, **30**:633-638

Sexton, D.J., and Spelman, D., (2003). Current best practices and guidelines: Assessment and management of complications in infective endocarditis. *Cardiol Clin,* **21**: 273–282

Shapira, Y., Weisenberg, D.E., Vaturi, M., (2007). The impact of intraoperative transesophageal echocardiography in infective endocarditis. *Isr Med Assoc J*, **9**: 299-302

Simsir, S.A., Cheeseman, S.H., Lancey, R.A., Vander Salm, T.J., and Gammie, J.S., (2003). Staged laparoscopic splenectomy and valve replacement in splenic abscess and infective endocarditis*. Ann Thoracic Surg,* **75**: 1635-1637

Skov, R.L., Sanden, A.K., Danchell, V.H., Robertsen, K., Ejlertsen, T., (1998). Systemic and deep-seated infection caused by Acranobacterium haemolyticum. *Eur J Clin Microbiol Infect Dis*, **17**: 578-582

Steckelberg, J.M., Murphy, J.G., Ballard, D., Bailey, K., Tajik, A.J., Taliercio, C.P., Giuliani, E.R., and Wilson, W.R., (1991). Emboli in infective endocarditis: The prognostic value of echocardiography*. Ann Intern Med,* **114**: 635–640

Stephens, J., (2004). Advanced Statistics Demystified. New York: Mc Graw Hill

Sternberg, S., (2004). Diagnostic Surgical Pathology**.** *Heart*, **40**:183-88

Thuny, F., Beurtheret, S., Mancini, J., (2011). The timing of surgery influences mortality and morbidity in adults with severe complicated infective endocarditis: A propensity analysis. *Eur Heart J*, **32**: 2027-33

Thuny, F., Habib, G., (2010). When should we operate on patients with acute infective endocarditis? *Heart*, **96**: 892-7

Vieira, M.L., Grinberg, M., Pomerantzeff, P.M., (2004). Repeated echocardiographic examinations of patients with suspected infective endocarditis. *Heart*, **90**:1020-4

Vikram, H.R, Buenconsejo, J., Hasbun, R., and Quagliearello, V.J., (2003). Impact of valve surgery on 6-month mortality in adults with complicated, left-sided native valve endocarditis: a propensity analysis*. JAMA,* **290**: 3207–3214

Vilacosta, I., Graupner, C., San Roman, J.A., Sarria, C., Ronderos, R., Fernandez, C., Mancini, L., Sanz, O., Sanmartin, J.V., and Stoermann, W., (2002). Risk of embolization after institution of antibiotic therapy for infective endocarditis*. J Am Coll Cardio,* **39**: 1489–1495

Vlessis, A.A., Hovaguimian, H., Jaggers, J., Ahmad, A., and Starr, A., (1996). Infective endocarditis: Ten-year review of medical and surgical therapy*. AnnThoracic Surg,* **61**: 1217–1222

Walkes, J.C., and Reardon, M.J., (2003). Current thinking in stentless valve surgery. *Curr Opin Cardiol*, **18**: 117–123

Weiss, S.W., and Goldblum, J.R., (2001). Weiss's soft tissue tumors. *Tumors,* **40**:205-210

Weiss, P.J., Kennedy, C.A., McCann, D.F., Hill, H.E., and Oldfield, E.C III., (1992). Fulminant endocarditis due to infection with penicillinase-producing Neisseria gonorrhoeae*. Sex Transm Dis,* **19**: 288–290

Werner, A.S., Cobbs, C.G., Kaye, D., and Hook, E.W., (1967). Studies on the bacteraemia of bacterial endocarditis. *JAM,* **202**: 199–2

Willemse, I., (2009). Statistical Methods and Calculations Skills. 3rd ed. Cape Town: Juta& Co

Wilson, W., Taubert, K.S., and Gewit, M., (2007). Prevention of infection endocarditis. *Endocarditis*,**15**: 1736-1754

APPENDICES

APPENDIX: A

April 2012 - June 2012

Introduction to proposal

Inspection of literature

Submission of proposal

September 2012 – April 2013

Collection of data

Checking of parameters

Analysis of data

May 2013 – June 2013

Compiling of all information

July 2013 - August 2013

Final write-up

Finding of errors and correcting of all information

Submitting dissertation for examination

Literature review and project write-up is ongoing

APPENDIX: B

FLOW CHART- SUMMARISING ACTIVITIES OF THE RESEARCH PROCESS

Patients with infective endocarditis coming for cardiac surgery

↓

Selection of patients is done using the inclusion and exclusion criteria

↓↓

Consent forms and information; patients not selected if they fall

into

letters issued by student/staff the exclusion criteria

↓↓

excluded from the study

↓

Written or verbal explanation of the study

will be given on request →→→

↓↓

Patient interested; patient unwilling to participate

↓

↓

→ Consent forms signed and handed

In for collection

↓↓

Patient has accepted and agreed; patient declined to be part of the

Study

↓

Research student plans out data collection clinical diagnosis, echocardiography and intraoperative results

Blood cultures taken by cardiologist

Echocardiogram to be performed by cardiac clinical technologist

During the operation it was confirmed whether there was a vegetation or not.

↓

Data collected to be analysed

↓

Statistical analysis and interpretation of data

↓

Final write-up, completion of thesis

APPENDIX: C

STATISTICAL ANALYSES

The Chairperson,
Medunsa Campus Research and Ethics Committee (MCREC),
Box _____
UNIVERSITY OF LIMPOPO
Medunsa Campus

Dear Sir/Madam

STATISTICAL ANALYSES

I have studied the research protocol of M.M.Henema

titled: Infective endocarditis at Dr George Mukhari Hospital: correlating Echocardiography findings with intra-operative findings (visual and Histology)

and I agree to assist with the statistical analyses.

Yours sincerely,

[redacted]
Signature: Statistician

M.M.Motshwane

Name in block letters

29 June 2012
Date

* Please delete which is not applicable. If you do not agree to assist with the statistical analyses, please provide reasons on a separate sheet.

10

APPENDIX: D

DURBAN UNIVERSITY of TECHNOLOGY

INSTITUTIONAL RESEARCH ETHICS COMMITTEE (IREC)

8 October 2012

IREC Reference Number: **REC 45/12**

Mr M M Henema
1400 Oliver Tambo Drive
P O Steadville
3373

Dear Mr Henema

Infective endocarditis at Dr George Mukhari Hospital: correlating echocardiography findings with intra-operative findings

I am pleased to inform you that Full Approval has been granted to your proposal REC 45/12.

The Proposal has been allocated the following Ethical Clearance number **IREC 039/12**. Please use this number in all communication with this office.

Approval has been granted for a period of one year, before the expiry of which you are required to apply for safety monitoring and annual recertification. Please use the Safety Monitoring and Annual Recertification Report form which can be found in the Standard Operating Procedures [SOP's] of the IREC. This form must be submitted to the IREC at least 3 months before the ethics approval for the study expires.

Any adverse events [serious or minor] which occur in connection with this study and/or which may alter its ethical consideration must be reported to the IREC according to the IREC SOP's. In addition, you will be responsible to ensure gatekeeper permission.

Please note that any deviations from the approved proposal require the approval of the IREC as outlined in the IREC SOP's.

Yours Sincerely

[redacted]

Dr D F Naude
Chairperson: IREC

APPENDIX: E

health and social development
Department: Health and Social Development
GAUTENG PROVINCE

DR GEORGE MUKHARI HOSPITAL

Enquiries: Dr. P. Shembe
Director: Clinical Services
Tel no: 012 529 3880
Fax no: 012 5600099

To : Mr. Musawenkosi Henema
Department of Cardiology
University of Limpopo
MEDUNSA
0208

Date : 30 May 2012

PERMISSION TO CONDUCT RESEARCH

The Dr. George Mukhari Hospital hereby grants you permission to conduct research on "A prospective study of infective endocarditis at Dr. George Mukhari Hospital: Correlating Echocardiography findings with intra-operative findings (visual and histology)".

This permission is granted subject to the following conditions:

☑ That you obtain Ethical Clearance from the Human Research Ethics Committee of the relevant University

☑ That the Hospital incurs no cost in the course of your research

☑ That access to the staff and patients at the Dr George Mukhari Hospital will not interrupt the daily provision of services.

☑ That prior to conducting the research you will liaise with the supervisors of the relevant sections to introduce yourself (with this letter) and to make arrangements with them in a manner that is convenient to the sections.

Yours sincerely

[redacted]

DR. P SHEMBE
DIRECTOR: CLINICAL SERVICES

APPENDIX: F

LETTER OF INFORMATION

DEAR PARTICIPANT

Welcome to my research project. Thank you for participating in my study.

Title of the Research Study: Infective Endocarditis at Dr George Mukhari Hospital: correlating Echocardiography findings with intra-operative findings

Principal Investigator/s/researcher: Musawenkosi Msizi Henema (B Tech: Clinical Technology; Contact number: 012-5293112)

Supervisor: Prof J K Adam (D Tech), Associate Professor, DUT (Contact number: 031-3735291)

Co-Supervisor: Prof P S Mntla (PhD) Head: Cardiology, Dr George Mukhari Hospital (Contact number: 012-5214627)

Brief Introduction and Purpose of the Study: Infective endocarditis is an infection of the endocardial valves, usually with bacteria or fungi. It causes fever, anaemia and myocardial abscess. The purpose is to compare the echocardiographic findings with intraoperative findings (histology and visual).

Outline of the Procedures:

a) A cardiologist will examine patients clinically for features of infective endocarditis. Blood will be sent to the laboratory for culture in order to detect the presence of micro-organisms. The researcher will perform an echocardiogram to assess which valve is affected, the ejection fraction and the size of the vegetation/mass or abscess.

b) For patients requiring heart surgery, the cardiac surgeon will perform the valve replacement, and the intra-operative findings will be assessed visually to confirm the presence of vegetation or abscesses and leaflet destruction. During the operation, which is done by a cardiac surgeon, a biopsy sample will be taken for histological examination to confirm the presence of vegetation or an abscess.

c) Thereafter, the cardiac surgeon will perform the valve repair/replacement/ bio prosthesis. The researcher will be blinded to the findings in the theatre, as the researcher will not be present in the theatre.

d) The results from the laboratory will be sent to the researcher. The researcher will then able to confirm if the presence of vegetation or a mass/abscess and leaf destruction.

The blood and other information obtained will be analysed by the principal investigator and information will be available to those concerned.

Inclusion criteria

1. All patients with infective endocarditis in the aortic, mitral or tricuspid valve requiring surgical intervention will be included in the study.
2. Adult patients ranging from 20-45 years.
3. Signed informed consent.

Exclusion criteria

1. Cardiac patients who have congenital heart diseases (e.g., ventricular septal defects, patent ductus arterioses, atrial septal defects).
2. Critically ill /unstable patients with infective endocarditis.
3. Patients with infective endocarditis of non-bacterial origin (e.g myxoma, viral and fungal).

Risks or Discomforts to the Participant: None

Benefits: Prioritising surgery for infective endocarditis patients post-echocardiogram.

Better analysis of your diagnosis and medical management of other patients.

Left ventricular function and outcome of surgical intervention in infective endocarditis patients.

Correlating surgical outcomes with echocardiograms findings.

Age and surgical outcomes in patients with infective endocarditis.

Reason/s why the Participant may Withdraw from the Study: Your participation in this study is voluntary and refusal to participate will not result in any adverse consequences.

Remuneration: You will not be awarded any remuneration for taking part in this study.

Costs of the Study: Your participation in this research is free of charge.

Confidentiality: Your personal information will be kept confidential by the use of a coding system for data analysis and reporting.

Research-related Injury: This needs to be reported to the DUT Institutional Research and Ethics Committee (IREC), so please ensure that you advise me of any such problems.

Persons to Contact in the Event of Any Problems or Queries:

Supervisors: Prof J K Adam (DUT) Tel: 031-373529

Prof P S Mntla (Dr George Mukhari Hospital) Tel: 012-5214627

IREC Research Administrator (DUT) Tel: 031-3732900

CONSENT

Statement of Agreement to Participate in the Research Study:

- I hereby confirm that I have been informed by the researcher, _Mr MMF Henema (name of researcher), about the nature, conduct, benefits and risks of this study - Research Ethics Clearance Number: _039/12,
- I have also received, read and understood the above written information (Participant Letter of Information) regarding the study.
- I am aware that the results of the study, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report.
- In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised system by the researcher.
- I may, at any stage, without prejudice, withdraw my consent and participation in the study.
- **I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study.**
- **I understand that significant new findings developed during the course of this research which may relate to my participation will be made available to me.**

_____ _____ _____ _____

Full Name of Participant **Date** **Time** **Signature/ Right Thumbprint**

I, Mr MMF Henema (name of researcher) herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

_____ _____ _____

Full Name of Researcher **Date** **Signature**

_____ _____ _____

Full Name of Witness (If applicable) Date Signature

_____ _____ _____

Full Name of Legal Guardian (If applicable) Date Signature

SETSWANA TRANSLATION

Karolwana A: Lekwalotshopo le tshopoboitlamo

BATSAKAROLO

Leamogetswe mopatlisesong projeking. Kelebogela batsakarolo mothutong yame.

SETLOGO PATLISISO BOITHUTO: Infective Endocarditis at Dr George Mukhari Hospital: correlating Echocardiography findings with intra-operative findings (visual and histology)

Mogolwanewa dipatlisiso: Musawenkosi Msizi Henema (Nomoro thuso: 012-5293112)

Motlhokomedi: Prof JK Adam, Modirisani Professor, DUT (Nomoro thuso: 031-3735291)

Modiri-motlhokomedi: Prof PS Mntla, Thlogoya Cardiology, Dr George Mukhari Hospital (Nomoro thuso: 012-5214627)

Matseno le maikaelelo a boithuto: Bolwetse bamogareg apelo bodirwang kedikoko anathloko mommeleng. Boithla gisa kamalwetse a mokgothlwane, boladomopelong le malwetse amang.Maikaelelo a boithutoke go aroganya dipontsho tsetlhagang momocheneng le dipatlisiso tsethlagang momolwetse aoperatilwe.

Lenaneo la Tsamayiso

a) Ngaka yadipelo etlathlathlo bamolwetsi go batlisisa dilemogo tsabolwetse jwapelo. Madi a tlaromelwa laborotori go fatolola le go lebelela matshwayo a dikokwana tsabolwetsejo.Modira patlisiso o tladiri sasonayapelo go lekola gore kekarolo efeyapelo e eamegileng le gore matla a peloe kabangkaona a kaakang, le bogolo ba sesakumopelong gore segodile go fithlelakae.
b) Go balwetse baba thlokangkaroyapelo, Ngakayadikaro e tla baakanya valve e amegilengkanakoyakaro, dipatlisisotse di bonweng, di tlalebedisiswaka go di bona go netefatsa gore sekaku se bonwelegorekaroloana ya valve esenyegile go fithlelakae. Kayonanakoyakarongaka o tlatsayalenathwana la nama go diradipatlisisotsedingwetsa go netefatsa gore sekakusetengkannete.
c) Moragogamo, ngakawadikarotsapelo o tlasimolla go baakanyakaroloana e eamegileng. Modirapatlisiso o tlabo a saitse gore godiregaeng, kaatlaboasatsenakamophaphosingyadikaro.
d) Dipholotsalaborotari di tlaromelwa go mothoyo o dirangdipatlisiso. Modiradipatlisisoetlanna gone a netefatsang gore sakakusetengmopelong.
e) Madi le dinthla tsedingwetse dibonweng ditlaleko lwakemobatlisisi o mogoloe begona kitsisoetlabonwakebao ba baethlokang.

<u>Batho ba bathlokagalang</u>

1. Balwetsebohle ba balwalang pelobathlokangkaro ba tla akaretswa mopatlisisong
2. Balwetse ba bagolo go tlogamodingwagengtse 20 go fithlela go 45yrs
3. Diforomotsagodumelanaebile e sayinilwe.

Batho ba basathlokegeng

1. Balwetse ba pelo babanalengbolwetsejwapeloyathlogo.
2. Balwetse ba balwalangthata.
3. Balwetse ba banalengbolwetsejobo ba fetele.

Tekelo: Gadiyo.

Dipoelo: Gogona go those kakaka nyoyabolwetse le gothose balwetsebabang le go tlhagisagotsa go neyatselaebotokayathlokomeloyabolwetse.

Lebakalelekadirang go re motseakarolo a ntshiwemopatlisisong: Go tse akarolo yagago keboineelo, go gana go tseakarolo go kase go bakele ditlamora gotsedileng kgathlanong le wena.

Tsadituelo: Motsakarolo aka sebonetuelo mokarolwa nengaedirelengga go ithuta.

Bolengjwamadi: Gotsakarolo mopatlisesong e gagoduelwesepe.

Go bana le siphiri: Karoloyatsa botshelo jwagago etlannase phirimothusongya system tebano le kitsokatoloso le go neelarepoto.

Go kabana le dipatlisisotebang le dikgobalo: Gobotlhokwa gore dipotsodilebisiwa go DUT moago, Karoloyadipatlisiso (IREC) le kopiwa gore de kakanyotebano le mathataotlhe le nkitsise.

Mothoyomalebamabapeng le dipotso:

Bagolwane ba di patlisiso:

Prof JK Adam (DUT) Nomoro thuso: 031-3735291

Prof PS Mntla (Dr George Mukhari Hospital) Nomoro thuso: 012-5214627

(IREC) Moago karoloyadipatlisiso le komittsamaiso (DUT) Nomoro thuso: 031-3732900

DURBAN UNIFESITI YA TEKINOLOGY

NTLOLOEAGO PATLISISO MOLAO KOMITI TSAMAISO (IREC)

MOLAO WATUMELELANO GO TSAYA KAROLO MODITHUTONG PATLISISO:

- .Kemogonetifatsa gore keitsesileina la mmatlisisi,tebang le tsatlhago,maitshwaro, ledipoelo le dikgoreletsomothutongpatlisisomotheo le nomoro _____,
- .Keamogetse,keboisetselegotlhaloganyatebang le dintlhatsekwadilwengtebang le goithuta.
- .Keelelewasentle gore dipholotsathuto e, diakaretsadintlhatsabotshelojwame, tsabonnajwame, dingwagatsamatsalo, letlhalamatsako, maina le gobatlisisabogolwanetebang le lefebarapotothuto.
- .Mabapi le patlisisodintlhatlhokego, kedumela gore dintlhapatlisisoditlangwakadikomputaka
- .Go kadirega, motsamaong, gorekwantle le kgapeletso, nkaboelamoragolegosetsweleletse dithutotsamepele.
- .Ke bone nakoentse go kabotsa dipotsiso le go netefatsa kgatlhegoyamegoka tsweleletsadithutotsame.
- .Kenetefaditse gore dipatlisisotsapatlisisoyadithutotseetselegonna le mosalathatamodipatlisisongtsame.

_____ _____ _____

Leina la motseakarolo. Letlha/Nako Mosaino

Nna_____kedumela gore motseyakarolotebang le patsisisothutoyatlhago o boleletse gore maitshwaro a gagwe a nnejangmothutong e.

_____ _____ _____

Leina la mobatlisisi Letlha Mosaino

_____ _____ _____

Leina la dipaki Letlha Mosaino

_____ _____ _____

Leina kabotlalomotlhopiwa

Motlhokomedi Letlha Mosaino

APPENDIX: G

The infective endocarditis patient's echocardiographical and clinical findings, intraoperative TEE (visual and histology).

Echocardiographical findings versus intraoperative findings (visual)

Patient 1		
	Echocardiographic	**Intraoperative (visual)**
Sex	1	1
Age (Years)	40	40
Left ven (end.diameter)	47	50
Left ven(ensyst diameter)	30	38
Ejection fraction (%)	77	70
Shortening fraction (%)	43	38
Affected valves	2	2
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia	X	
Fever	X	
Finger clubbing		X
Splenomegaly		X
Changing or new murmurs		X
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 2		
	Echocardiographic	**Intraoperative (visual)**
Sex	2	2
Age (Years)	23	23
Left ven (end.diam)	50	55
Left ven(ensyst.diam)	32	30
Ejection fraction (%)	67	75
Shortening fraction (%)	37	40
Affected valves	3	3
Vegetation/mass/abscess/	2	2
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia	X	
Fever	X	
Finger clubbing		X
Splenomegaly		X
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Fungal

Echocardiographical findings versus intraoperative findings (visual)

Patient 3		
	Echocardiographic	**Intraoperative (visual)**
Sex	2	2
Age (Years)	28	28
Left ven (end.diam)	52	45
Left ven(ensyst.diam)	38	30
Ejection fraction (%)	60	60
Shortening fraction (%)	31	30
Affected valves	3	3
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia	X	
Fever	X	
Finger clubbing		X
Splenomegaly		X
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Rheumatic, bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 4		
	Echocardiographic	**Intraoperative (visual)**
Sex	1	1
Age (Years)	43	43
Left ven (end.diam)	50	50
Left ven(ensyst.diam)	30	29
Ejection fraction (%)	67	70
Shortening fraction (%)	34	35
Affected valves	2	2
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia		X
Fever	X	
Finger clubbing	X	
Splenomegaly	X	
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 5		
	Echocardiographic	**Intraoperative (visual)**
Sex	2	2
Age (Years)	24	24
Left ven (end.diam)	61	70
Left ven(ensyst.diam)	40	40
Ejection fraction (%)	50	45
Shortening fraction (%)	25	22
Affected valves	3	4
Vegetation/mass/abscess/	1	1
Leaflets destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia		X
Fever	X	
Finger clubbing		
Splenomegaly		
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Rheumatic, fungal

Echocardiographical findings versus intraoperative findings (visual)

Patient 6		
	Echocardiographic	**Intraoperative (visual)**
Sex	2	2
Age (Years)	22	22
Left ven (end.diam)	51	50
Left ven(ensyst.diam)	34	39
Ejection fraction (%)	60	68
Shortening fraction (%)	34	35
Affected valves	3	3
Vegetation/mass/abscess/	2	2
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia		X
Fever	X	
Finger clubbing	X	
Splenomegaly	X	
Changing or new murmurs		X
Evidence of cardiac embolism		X

Intraoperative findings (histology)

Histology	Mitral valve degeneration Barlow disease

Echocardiographical findings versus intraoperative findings (visual)

Patient 7		
	Echocardiographic	**Intra-operative (visual)**
Sex	1	1
Age (Years)	37	37
Left ven (end.diam)	80	70
Left ven(ensyst.diam)	59	40
Ejection fraction (%)	21	19
Shortening fraction (%)	10	8
Affected valves	3	3
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia	X	
Fever	X	
Finger clubbing	X	
Splenomegaly		X
Changing or new murmurs		X
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Rheumatic, fungal

Echocardiographical findings versus intraoperative findings (visual)

Patient 8		
	Echocardiographic	**Intra-operative (visual)**
Sex	1	1
Age (Years)	44	44
Left ven (end.diam)	46	40
Left ven(ensyst.diam)	23	20
Ejection fraction (%)	68	75
Shortening fraction (%)	34	39
Affected valves	3	3
Vegetation/mass/abscess/	2	2
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia	X	
Fever	X	
Finger clubbing		X
Splenomegaly	X	
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 9		
	Echocardiographic	**Intra-operative (visual)**
Sex	1	1
Age (Years)	37	37
Left ven (end.diam)	51	39
Left ven(ensyst.diam)	30	19
Ejection fraction (%)	66	70
Shortening fraction (%)	32	40
Affected valves	2	
Vegetation/mass/abscess/	1	
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia		X
Fever	X	
Finger clubbing	X	
Splenomegaly	X	
Changing or new murmurs		X
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 10		
	Echocardiographic	**Intra-operative (visual)**
Sex	1	1
Age (Years)	26	26
Left ven (end.diameter)	51	48
Left ven(ensyst diameter)	31	27
Ejection fraction (%)	61	70
Shortening fraction (%)	30	40
Affected valves	2	2
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia	X	
Fever	X	
Finger clubbing		X
Splenomegaly	X	
Changing or new murmurs	X	
Evidence of cardiac embolism		X

Intraoperative findings (histology)

Histology	Bacterial

Echocardiographical findings versus Intraoperative findings (visual)

Patient 11		
	Echocardiographic	**Intra-operative (visual)**
Sex	2	2
Age (Years)	32	32
Left ven (end.diameter)	47	50
Left ven(ensyst diameter)	23	30
Ejection fraction (%)	58	62
Shortening fraction (%)	29	38
Affected valves	2	2
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia	X	
Fever	X	
Finger clubbing	X	
Splenomegaly		X
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 12		
	Echocardiographic	**Intra-operative (visual)**
Sex	1	1
Age (Years)	30	30
Left ven (end.diameter)	43	39
Left ven(ensyst diameter)	27	20
Ejection fraction (%)	66	78
Shortening fraction (%)	32	40
Affected valves	2	2
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia	X	
Fever	X	
Finger clubbing		X
Splenomegaly		X
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 13		
	Echocardiographic	**Intra-operative (visual)**
Sex	1	1
Age (Years)	41	41
Left ven (end.diameter)	58	65
Left ven(ensyst diameter)	41	50
Ejection fraction (%)	40	30
Shortening fraction (%)	25	12
Affected valves	3	4
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia		X
Fever	X	
Finger clubbing	X	
Splenomegaly		X
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Rheumatic, bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 14		
	Echocardiographic	**Intra-operative (visual)**
Sex	1	1
Age (Years)	43	43
Left ven (end.diameter)	49	55
Left ven(ensyst diameter)	30	38
Ejection fraction (%)	61	75
Shortening fraction (%)	30	40
Affected valves	3	3

Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia	X	
Fever	X	
Finger clubbing	X	
Splenomegaly		X
Changing or new murmurs	X	
Evidence of cardiac embolism		X

Intraoperative findings (histology)

Histology	Rheumatic, fungal

Echocardiographical findings versus intraoperative findings (visual)

Patient 15		
	Echocardiographic	**Intra-Operative (visual)**
Sex	2	2
Age (Years)	21	21
Left ven (end.diameter)	50	57
Left ven(ensyst diameter)	31	39
Ejection fraction (%)	60	70
Shortening fraction (%)	30	41
Affected valves	2	2
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia	X	
Fever	X	
Finger clubbing		X
Splenomegaly		X
Changing or new murmurs		X
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 16		
	Echocardiographic	**Intra-operative (visual)**
Sex	1	1
Age (Years)	32	32
Left ven (end.diameter)	58	62
Left ven(ensyst diameter)	49	50
Ejection fraction (%)	34	29
Shortening fraction (%)	17	10
Affected valves	4	4
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia	X	
Fever	X	
Finger clubbing	X	
Splenomegaly	X	
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Rheumatic, bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 17		
	Echocardiographic	**Intra-operative (visual)**
Sex	1	1
Age (Years)	21	21
Left ven (end.diameter)	49	52
Left ven(ensyst diameter)	27	30
Ejection fraction (%)	76	70
Shortening fraction (%)	45	40
Affected valves	3	3
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia	X	
Fever	X	
Finger clubbing	X	
Splenomegaly		X
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Rheumatic, bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 18		
	Echocardiographic	**Intra-operative (visual)**
Sex	1	1
Age (Years)	32	32
Left ven (end.diameter)	61	60
Left ven(ensyst diameter)	42	40
Ejection fraction (%)	58	50
Shortening fraction (%)	35	38
Affected valves	3	3
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	Yes	No
Anaemia	X	
Fever	X	
Finger clubbing		X
Splenomegaly	X	
Changing or new murmurs		X
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Rheumatic, bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 19		
	Echocardiographic	Intra-operative (visual)
Sex	2	2
Age (Years)	40	40
Left ven (end.diameter)	53	50
Left ven(ensyst diameter)	39	42
Ejection fraction (%)	53	40
Shortening fraction (%)	27	20
Affected valves	3	3
Vegetation/mass/abscess/	4	4
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	Yes	No
Anaemia	X	
Fever	X	
Finger clubbing		X
Splenomegaly	X	
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Myxomatous

Echocardiographical findings versus intraoperative findings (visual)

Patient 20		
	Echocardiographic	Intra-operative (visual)
Sex	1	1
Age (Years)	38	38
Left ven (end.diameter)	61	60
Left ven(ensyst diameter)	40	50
Ejection fraction (%)	62	70
Shortening fraction (%)	31	40
Affected valves	1	1
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	Yes	No
Anaemia		X
Fever	X	
Finger clubbing	X	
Splenomegaly		X
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Rheumatic, bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 21		
	Echocardiographic	**Intraoperative (visual)**
Sex	2	2
Age (Years)	30	30
Left ven (end.diameter)	73	70
Left ven(ensyst diameter)	45	40
Ejection fraction (%)	67	73
Shortening fraction (%)	38	40
Affected valves	3	3
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia		X
Fever	X	
Finger clubbing		X
Splenomegaly	X	
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Rheumatic, bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 22		
	Echocardiographic	**Intra-operative (visual)**
Sex	1	1
Age (Years)	23	23
Left ven (end.diameter)	60	70
Left ven(ensyst diameter)	47	50
Ejection fraction (%)	55	50
Shortening fraction (%)	24	20
Affected valves	1	1
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia	X	
Fever	X	
Finger clubbing	X	
Splenomegaly	X	
Changing or new murmurs		X
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Rheumatic, bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 23		
	Echocardiographic	**Intra-operative (visual)**
Sex	1	1
Age (Years)	34	34
Left ven (end.diam)	55	45
Left ven(ensyst diam)	34	30
Ejection fraction (%)	50	40
Shortening fraction (%)	26	20
Affected valves	3	3
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia		X
Fever	X	
Finger clubbing	X	
Splenomegaly	X	
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Rheumatic, bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 24		
	Echocardiographic	**Intra-operative (visual)**
Sex	1	1
Age (Years)	20	20
Left ven (end.diam)	50	44
Left ven(ensyst diam)	39	30
Ejection fraction (%)	58	50
Shortening fraction (%)	29	30
Affected valves	3	3
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia	X	
Fever	X	
Finger clubbing	X	
Splenomegaly	X	
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Rheumatic, fungal

Echocardiographical findings versus intraoperative findings (visual)

Patient 25		
	Echocardiographic	**Intra-operative (visual)**
Sex	1	1
Age (Years)	24	24
Left ven (end.diam)	50	40
Left ven(ensyst.diam)	37	29
Ejection fraction (%)	68	75
Shortening fraction (%)	34	39
Affected valves	3	3
Vegetation/mass/abscess/	3	3
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	Yes	No
Anaemia		X
Fever	X	
Finger clubbing	X	
Splenomegaly	X	
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Mitral valve degeneration Barlow's disease

Echocardiographical findings versus intraoperative findings (visual)

Patient 26		
	Echocardiographic	**Intra-operative (visual)**
Sex	1	1
Age (Years)	28	28
Left ven (end.diam)	50	45
Left ven(ensyst diam)	38	30
Ejection fraction (%)	60	70
Shortening fraction (%)	32	45
Affected valves	1	1
Vegetation/mass/abscess/	3	3
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia	X	
Fever	X	
Finger clubbing		X
Splenomegaly		X
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Tumour fibro elastosiscontangiosum

Echocardiographical findings versus intraoperative findings (visual)

Patient 27		
	Echocardiographic	**Intra-operative (visual)**
Sex	1	1
Age (Years)	37	37
Left ven (end.diam)	47	55
Left ven(ensyst diam)	29	38
Ejection fraction (%)	60	58
Shortening fraction (%)	32	35
Affected valves	3	3
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia	X	
Fever	X	
Finger clubbing	X	
Splenomegaly	X	
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Rheumatic, bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 28		
	Echocardiographic	**Intra-operative (visual)**
Sex	2	2
Age (Years)	25	25
Left ven (end.diam)	73	69
Left ven(ensyst.diam)	47	41
Ejection fraction (%)	64	70
Shortening fraction (%)	36	43
Affected valves	2	2
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia	X	
Fever	X	
Finger clubbing	X	
Splenomegaly		X
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 29		
	Echocardiographic	**Intra-operative (visual)**
Sex	2	2
Age (Years)	32	32
Left ven (end.diam)	60	65
Left ven(ensyst.diam)	35	41
Ejection fraction (%)	57	50
Shortening fraction (%)	24	26
Affected valves	1	1
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia	X	
Fever	X	
Finger clubbing	X	
Splenomegaly	X	
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 30		
	Echocardiographic	**Intra-operative (visual)**
Sex	2	2
Age (Years)	24	24
Left ven (end.diam)	42	40
Left ven(ensyst.diam)	27	22
Ejection fraction (%)	65	70
Shortening fraction (%)	35	40
Affected valves	3	3
Vegetation/mass/abscess/	3	3
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia	X	
Fever	X	
Finger clubbing		X
Splenomegaly		X
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Calcification, mitral valve degeneration Barlow disease

Echocardiographical findings versus intraoperative findings (visual)

Patient 31		
	Echocardiographic	**Intra-operative (visual)**
Sex	2	2
Age (Years)	25	25
Left ven (end.diam)	49	55
Left ven(ensyst.diam)	27	29
Ejection fraction (%)	70	60
Shortening fraction (%)	41	35
Affected valves	2	2
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia		X
Fever	X	
Finger clubbing	X	
Splenomegaly	X	
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 32		
	Echocardiographic	**Intra-operative (visual)**
Sex	1	1
Age (Years)	42	42
Left ven (end.diam)	38	40
Left ven(ensyst.diam)	19	22
Ejection fraction (%)	78	68
Shortening fraction (%)	44	37
Affected valves	3	3
Vegetation/mass/abscess/	3	2
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia		X
Fever	X	
Finger clubbing	X	
Splenomegaly		X
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Bacterial, mitral valve degeneration Barlow disease

Echocardiographical findings versus intraoperative findings (visual)

Patient 33		
	Echocardiographic	**Intra-operative (visual)**
Sex	2	2
Age (Years)	28	28
Left ven (end.diam)	62	63
Left ven(ensyst.diam)	44	40
Ejection fraction (%)	54	50
Shortening fraction (%)	29	25
Affected valves	1	1
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia	X	
Fever	X	
Finger clubbing		X
Splenomegaly		X
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Rheumatic, bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 34		
	Echocardiographic	**Intra-operative (visual)**
Sex	2	2
Age (Years)	29	29
Left ven (end.diam)	61	59
Left ven(ensyst.diam)	37	35
Ejection fraction (%)	68	75
Shortening fraction (%)	37	39
Affected valves	3	3
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia		X
Fever	X	
Finger clubbing		X
Splenomegaly		X
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Rheumatic, bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 35		
	Echocardiographic	**Intra-operative (visual)**
Sex	2	2
Age (Years)	42	42
Left ven (end.diam)	59	65
Left ven(ensyst.diam)	41	49
Ejection fraction (%)	58	50
Shortening fraction (%)	30	25
Affected valves	3	3
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia	X	
Fever	X	
Finger clubbing		X
Splenomegaly		X
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Rheumatic, bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 36		
	Echocardiographic	**Intra-operative (visual)**
Sex	1	1
Age (Years)	44	44
Left ven (end.diam)	48	50
Left ven(ensyst.diam)	20	25
Ejection fraction (%)	68	78
Shortening fraction (%)	38	41
Affected valves	1	1
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia		X
Fever	X	
Finger clubbing		X
Splenomegaly	X	
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Rheumatic, bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 37		
	Echocardiographic	**Intra-operative (visual)**
Sex	2	2
Age (Years)	31	31
Left ven (end.diam)	60	65
Left ven(ensyst.diam)	47	50
Ejection fraction (%)	30	25
Shortening fraction (%)	15	10
Affected valves	3	3
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	Yes	No
Anaemia	X	
Fever	X	
Finger clubbing	X	
Splenomegaly		X
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Rheumatic, bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 38		
	Echocardiographic	**Intra-operative (visual)**
Sex	1	1
Age (Years)	33	33
Left ven (end.diam)	54	50
Left ven(ensyst.diam)	38	30
Ejection fraction (%)	60	73
Shortening fraction (%)	37	41
Affected valves	3	3
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia		X
Fever	X	
Finger clubbing	X	
Splenomegaly		X
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Rheumatic, bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 39		
	Echocardiographic	**Intra-operative (visual)**
Sex	1	1
Age (Years)	24	24
Left ven (end.diam)	47	55
Left ven(ensyst.diam)	29	35
Ejection fraction (%)	68	70
Shortening fraction (%)	34	35
Affected valves	2	2
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia	X	
Fever	X	
Finger clubbing		X
Splenomegaly		X
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Bacterial

Echocardiographical findings versus intraoperative findings (visual)

Patient 40		
	Echocardiographic	**Intra-operative (visual)**
Sex	2	2
Age (Years)	34	34
Left ven (end.diam)	44	40
Left ven(ensyst.diam)	28	22
Ejection fraction (%)	58	62
Shortening fraction (%)	29	33
Affected valves	2	2
Vegetation/mass/abscess/	1	1
Leaflet destruction		

Clinical diagnosis

Clinical diagnosis	**Yes**	**No**
Anaemia		X
Fever	X	
Finger clubbing		X
Splenomegaly		X
Changing or new murmurs	X	
Evidence of cardiac embolism	X	

Intraoperative findings (histology)

Histology	Bacterial

APPENDIX: H

The dissertation titled

INFECTIVE ENDOCARDITIS AT DR GEORGE MUKHARI HOSPITAL: CORRELATING ECHOCARDIOGRAPHY FINDINGS WITH INTRAOPERATIVE FINDINDS (VISUAL AND HISTOLOGY)

by

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was submitted to me for language editing, which was completed on 13 April 2015.

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13 April 2015