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Efficacy of surgical and medical intervention for treatment of left-sided endocarditis

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BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

**EFFICACY OF SURGICAL AND MEDICAL INTERVENTION
FOR TREATMENT OF LEFT-SIDED ENDOCARDITIS**

by

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B.S., Northeastern University, 2016

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requirements for the degree of
Master of Science

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For my friends and family who helped and supported me on this journey

EFFICACY OF SURGICAL AND MEDICAL INTERVENTION

FOR TREATMENT OF LEFT-SIDED ENDOCARDITIS

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ABSTRACT

Background

Treatment of left-sided Infective Endocarditis (IE) is challenging due to the presence of both surgical and medical interventions. The choice typically depends on the patient's surgical risk and severity of infection. Our aim is to compare outcomes of IE patients who undergo valve replacement surgery with patients who are treated with solely antibiotics.

Methods

Patients undergoing valve surgery at our institution from 1995 to 2014 (n=196) and patients who were treated medically for IE from 2001 to 2014 (n=120) were included in this study. In total, 316 patients were included and clinical data was retrospectively collected from chart review. Society of Thoracic Surgeons (STS) Scores were calculated to assess for surgical risk and data for preoperative fever, angina, and abscess was collected to assess for severity of infection. The primary outcome of interest was mortality at 30 days and 1 year post-treatment and secondary outcomes included post-treatment development of septic shock, MI, embolic events, recurrence of infection, stroke, and renal dysfunction. Cox regression analyses were performed to assess the

likelihood of mortality based on the patient's pre-intervention comorbidities and characteristics. A Kaplan-Meier Analysis was also conducted to assess for survival at both 30 days and 1 year.

Results

Pre-operative fever (68.88% surgical vs 52.50% medical, $p=0.002$), angina (13.78% surgical vs 2.50% medical, $p<0.05$), and presence of abscess (33.37% surgical vs 6.67% medical, $p<0.05$) were significantly higher in the surgical population. Mortality at both 30-days (7.65% surgical vs 29.17% medical, $p<0.05$) and 1 year (17.35% surgical vs 46.67% medical, $p<0.05$) was significantly higher in the medical cohort. Mortality in patients presenting with valvular abscess was significantly higher in the surgical population at 30 days (4.5% surgical vs 62.5% medical, $p<0.05$) and 1 year (15.15% surgical vs. 75.00% medical, $p<0.05$). Surgical risk was significantly higher in medical patients overall ($p<0.05$), but not significantly higher in the pathogen specific subgroups. By individual pathogen, medical mortality was significantly higher at both 30 days and 1 year in the MRSA ($p=0.0004$ and $p=0.0002$) and Staphylococcus population ($p=0.001$ and $p=0.0005$) but only significantly higher in the Streptococcus population at 1 year ($p=0.032$).

Conclusion

Valve Replacement Surgery in patients with left-sided MRSA and non-MRSA Staphylococcus IE leads to significantly better mortality outcomes at 30 days and 1 year than medical management. Specifically, we suggest that patients with preoperative

valvular abscess undergo valve replacement surgery, regardless of pathogen, and that patients with MRSA and non-MRSA Staphylococcus IE be strongly considered for surgical intervention.

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LIST OF ABBREVIATIONS

AFIB.....	Atrial Fibrillation
ARR.....	Aortic Root Replacement
AV.....	Atrio-Ventricular
AVR.....	Aortic Valve Replacement
AVr.....	Aortic Valve Repair
BNP.....	B-Type Natriuretic Peptide
CABG.....	Coronary Artery Bypass Graft
CHF.....	Congestive Heart Failure
COPD.....	Chronic Obstructive Pulmonary Disease
CVA.....	Cerebral Vascular Accident
DM.....	Diabetes Mellitus
ESRD.....	End Stage Renal Disease
HTN.....	Hypertension
IE.....	Infective Endocarditis
MI.....	Myocardial Infarction
MRSA.....	Methicillin-Resistant Staphylococcus Aureus
MVR.....	Mitral Valve Replacement
MVr.....	Mitral Valve Repair
NBT.....	Non-Bacterial Thrombus
PICC.....	Peripherally Inserted Central Catheter
RHD.....	Rheumatic Heart Disease

STS.....Society of Thoracic Surgeons
TEE Transesophageal Echocardiogram
TTE Transthoracic Echocardiogram

INTRODUCTION

Infective Endocarditis (IE) is a microbial infection of the inner lining of the heart, the endocardium. IE is typically caused by bacteria that travel through the blood and settle on the heart valves. IE is a very rare disease that affects less than 1% of the population, but once contracted, it holds a 1-year mortality rate of 40% (Kiefer et al., 2011).

The presence of bacteria in the blood is called bacteremia. Once bacteria has entered the bloodstream, there is potential for bacteria to deposit on any one of the cardiac valves and form a bacterial vegetation. Bacteria can enter the body during a surgery, a dental procedure, or by the use of contaminated needles when injecting IV drugs. Although blood is constantly flowing through the cardiac valves, they do not receive a devoted blood supply, which makes it very difficult for the body's immune system to combat a bacterial vegetation. This risk of bacterial deposition greatly increases if the patient's cardiac valve is already damaged, such as a patient presenting with a bicuspid aortic valve or a mitral valve prolapse (Vallejo, 2016).

Cardiac Anatomy

The heart consists of a series of chambers that synergistically work to pump blood throughout the body and the lungs. It consists of two smaller chambers called atria and two larger chambers called ventricles. Deoxygenated blood enters into the right atrium via the vena cava and passes through the tricuspid valve into the right ventricle. The right side of the heart deals solely with deoxygenated blood returning from the periphery and

pumps this blood into the pulmonary system through the pulmonary valve to become oxygenated. The oxygenated blood returns to the left atrium via the four pulmonary veins and is pumped through the mitral valve into the left ventricle. Finally, the blood is pumped up through the aortic valve into the aorta and to the rest of body.

The four cardiac valves play a major role in the proper movement and pumping of blood in this system. They act as one-way conduits that prevent the backflow of blood into the previous chamber. Valves are thin pieces of endocardium that consist of either two or three distinct leaflets. They are rooted tightly in the annulus fibrosus and are tethered to the cardiac skeleton so that they maintain their position.

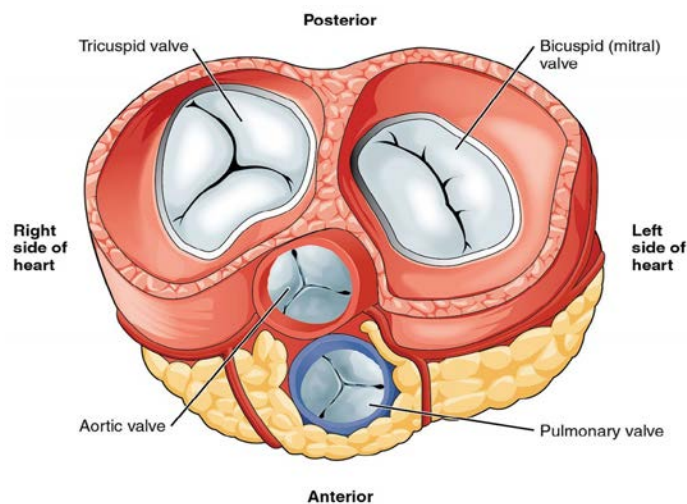


Figure 1: Transverse Section of Heart. This transverse section of the heart highlights the four cardiac valves and their position in the heart. It denotes the varying number of leaflets and the way the valves are seated in the cardiac anatomy. Figure taken from Teachmeanatomy.info

The two atrio-ventricular (AV) valves are the mitral and tricuspid valves and as their name implies, separate the atria from the ventricles. The AV valves are attached to papillary muscles in the right and left ventricles via chordae tendinae that aid them in their proper functioning. The chordae tendinae and papillary muscles ensure that the valves close properly and do not protrude, or prolapse, into the atria. During ventricular diastole, the pressure in the atria surpasses the pressure in the ventricles and this pressure pushes open the valves to allow blood to flow into the ventricles. Once the blood has entered the ventricles, the valves close to prevent any backflow. The closure of the AV valves is noted as the first heart sound, commonly referred to as the “lub”.

Once blood has entered the ventricles, focus shifts to the aortic and pulmonary valves, which are known as semilunar valves. These two valves do not have any chordae tendinae or papillary muscle attachments and open and close solely based on pressure changes in the heart. Pressure begins to rise in the ventricles and once that pressure eclipses the pressure in the aorta or pulmonary artery, the semilunar valves open and the ventricles contract, propelling blood to the body or pulmonary system. The closure of the semilunar valves is noted as the second heart sound, commonly referred to as the “dub”.

The tricuspid, pulmonary, and aortic valve all contain three leaflets are referred to as tricuspid valves while the mitral valve contains only two leaflets and is referred to as the bicuspid valve. The differences in pressure are important to the location of the bacterial vegetation in IE and will be discussed in detail in another section.

Valvular Pathology

The cardiac valves are all susceptible to disease. The most common valvular pathologies are stenosis and regurgitation/insufficiency. Stenosis is the narrowing of the valves due to the accumulation of calcification on the leaflets. This is typically an age-related process and can cause angina, syncope, or congestive heart failure (Rogers, 2013). Regurgitation/insufficiency is the backflow or leaking of blood into the prior cardiac chamber. This is also an age-related process but is commonly attributed to the dilation of annulus fibrosis that prohibits the valves to closing properly (Maurer, 2006). The presence of any of these pathologies facilitates the formation of a bacterial vegetation on the cardiac valves.

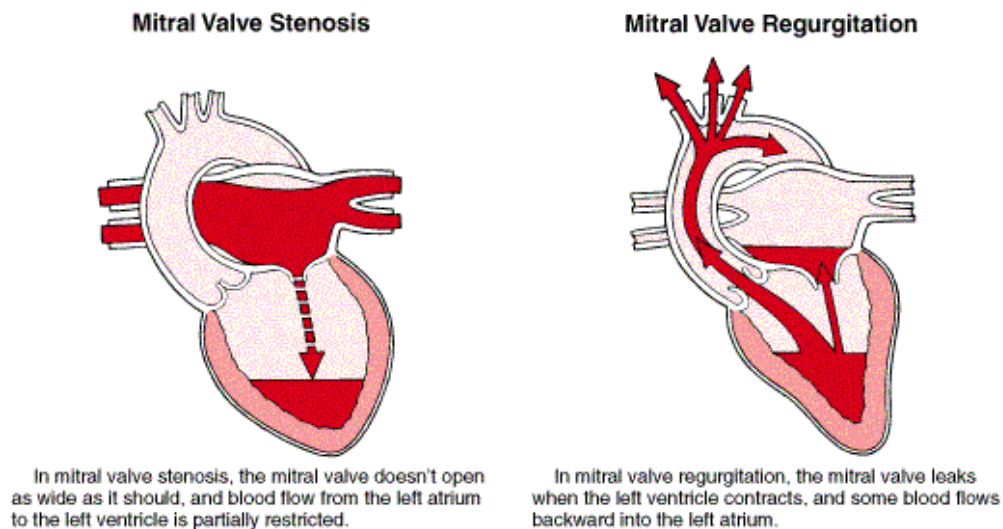


Figure 2: Mitral Valve Stenosis and Regurgitation. These images represent stenosis and regurgitation of the mitral valve. Mitral valve stenosis depicts the blood having a difficult time entering the left ventricle from the left atrium. Mitral valve regurgitation highlights the backflow of blood from the left ventricle to the left atrium. Figure taken from heartsurgeryinfo.com

Classifications of IE

IE is mainly classified as native or prosthetic IE. This classification aids in determining how the infection was acquired and determines how IE should be treated. Prosthetic valve endocarditis can be further broken down into early and late endocarditis. Early prosthetic valve endocarditis is defined as infection contracted less than 1 year from the operation and late prosthetic valve endocarditis is contracted more than 1 year post-op (Nonaka et al., 2013). Early prosthetic valve endocarditis is associated with a higher rate of heart failure and mortality and patients should be monitored closely post-op to avoid the development of early prosthetic valve IE (Castillo et al., 2004). The type of prosthetic valve that patients receive also impacts the risk of acquiring IE post op, as mechanical valves have a significantly higher rate of endocarditis at 1 year than bioprosthetic valves (Lund & Bland, 2006). Additionally, it is also important to determine if a patient has contracted right or left sided endocarditis. Right sided endocarditis is limited to tricuspid and pulmonic valve infection and left sided endocarditis includes the mitral and aortic valve. Patients who have left sided endocarditis have significantly worse preoperative conditions and also worse clinical outcomes post-operatively (Kamaledeen, Young, & Attia, 2012; Musci et al., 2007). Furthermore, IE used to be subdivided into acute and subacute classifications. These classifications attempted to reflect the severity and progression of the IE. Subacute IE was defined as a milder strain of infection and acute IE was characterized as more volatile and severe. Presently, this classification is not used due to its inaccuracy in the clinical setting (Morris, 2006). Physicians now prefer to use the terms short and long

incubation when characterizing IE, with short incubation signifying an infection of less than six weeks and long incubation signifying an infection of more than six weeks (Morris, 2006). The final classification of IE that is used clinically is characterizing the infection by pathogen. This system is valuable to physicians as they seek to treat IE because it is paramount to identify the invading pathogen to best treat the infection. The pathogen is confirmed via a blood culture test and the therapeutic course is then discussed. The most common pathogens found in IE are Streptococcus and Staphylococcus (Mostaghim, Lo, & Khardori, 2017). Staphylococcus IE is associated with a more severe preoperative presentation than non Staphylococcus IE (Han et al., 2017; Miro et al., 2005).

Risk Factors, Pathogenesis, and Symptoms of IE

The chance of contracting IE increases with several key risk factors. Congenital heart defects, rheumatic heart disease, and valve diseases are all contributors to the development of IE. Congenital heart defects, such as a bicuspid aortic valve and patent ductus arteriosus, are responsible for approximately 15% of all IE cases (Braunwald & Bonow, 2012). Studies have also shown that approximately 5% of patients with Rheumatic Heart Disease (RHD) develop IE (Okello et al., 2013). RHD, which is damage to the cardiac valves, develops after a patient is diagnosed with rheumatic fever and is typically treated with valve replacement surgery. If a patient does not have a congenital heart defect or was diagnosed with rheumatic fever earlier in life and they develop valvular regurgitation or stenosis, they are diagnosed with valve disease and are also susceptible to the development of IE. The diseased valves facilitate the attachment of

bacteria due to the presence of a non-bacterial thrombus (NBT). Once a patient presents with left-sided (aortic and mitral) regurgitation, there is endocardial damage that occurs at the site of both of these valves. This endocardial damage attracts platelets and fibrin to the site which form a clot, called NBT, and is the location to which bacteria can deposit if they enter the bloodstream. The NBT forms on the side of the valve that is exposed to lower pressure due to the Venturi Effect, which states that in a narrow space, fluid pressure decreases with a higher velocity. This principle pushes the NBT to the valvular chamber with lower pressure. In mitral valve endocarditis, the vegetation will develop on the atrial side of the mitral valve since that atrium has a lower pressure than the ventricle. In aortic valve endocarditis, the vegetation will develop on the ventricular side of the aortic valve since the left ventricle has a lower pressure than the aorta.

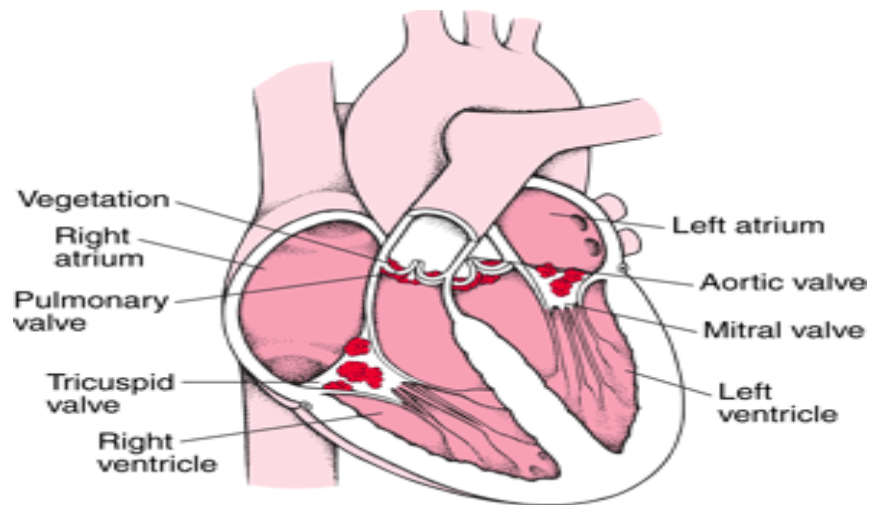


Figure 3: Location of Vegetations on the Cardiac Valves. This image represents the location of the IE on the four cardiac valves. All of the vegetations depicted are situated on the lower pressure side of the two chambers in question. As discussed above, the left atrium has a lower pressure than the left ventricle and therefore the IE develops on the atrial side. Figure taken from merckmanuals.com

If a patient who has a valve disease with a NBT is exposed to bacteria that enters their bloodstream, there is potential for that bacteria to attach onto the NBT and form a bacterial vegetation. The bacteria colonizes the NBT and the patient contracts IE and presents with numerous symptoms that aid in the diagnosis of IE.



Figure 4: Transesophageal Echocardiogram (TEE) of Mitral Valve Endocarditis. This TEE depicts the location of a vegetation on the mitral valve. This vegetation is located on the atrial side of the valve and is pushed to the side of the valvular opening, away from the center. This is consistent with the principles described in the Venturi Effect. Figure taken from sciencedirect.com

Patients with IE present with a myriad of symptoms. Fever, fatigue, and the development of a new cardiac arrhythmia are common (Vallejo, 2016). Angina, shortness of breath, and the heart failure have also been observed (Mostaghim et al., 2017). Since the cardiac valves constantly open and close, there is a high risk that a piece of bacteria can detach from a vegetation and embolize. This is very dangerous as this embolus can

cause an infarct if it lodges in a major blood vessel of organ. Left-sided vegetations typically embolize to the spleen, kidney, or the brain and can cause a stroke or severe organ failure (Ferro & Fonseca, 2014). Furthermore, Janeway lesions, glomerulonephritis, Osler nodes, and Roth spots have been seen in patients with IE. Janeway lesions are erythematous lesions that appear on your palms and your feet (Divakaramenon, 2005). They arise due to chronic bacterial infection and are hallmarks in the presentation of IE. Glomerulonephritis is a disease of the kidney that affects the kidney's filtration ability. Glomerulonephritis develops as a result of an embolus from a bacterial vegetation that lodges in the kidney (Boils, Nasr, Walker, Couser, & Larsen, 2015). It can cause short term necrosis and if the damage is serious and prolonged, can lead to chronic kidney disease (Boils et al., 2015). Osler nodes, similar to Janeway lesions, are lesions that develop on the palms and feet due to increased immunological activity. They differentiate themselves from Janeway lesions in that they are considered to be tender to the touch, while the Janeway lesions are not (Farrior & Silverman, 1976). Finally, Roth spots are white centered retinal hemorrhages that present due to increased immune activity (Mahroo & Graham, 2014).

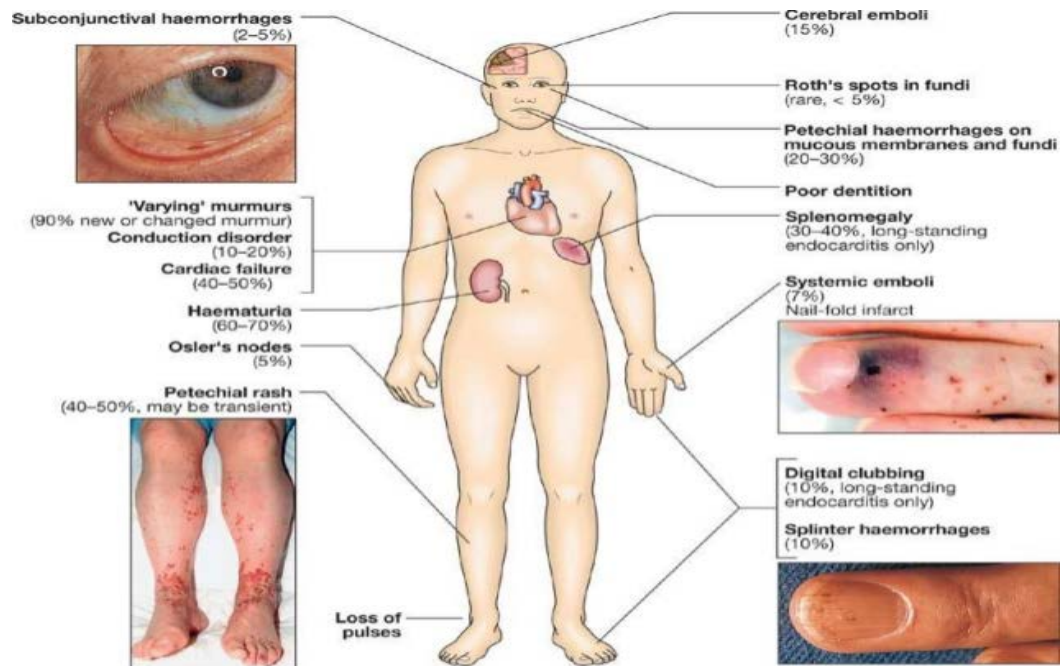


Figure 5: Clinical Manifestations of Infective Endocarditis. This image represents the clinical manifestations of the IE. The impact of this infection is not limited to the cardiovascular system and has wide reaching effects. All of these symptoms and presentations aid physicians in diagnosing IE. Figure taken from slideshare.net

Diagnosis of IE

The presence of the aforementioned symptoms as well as a thorough patient history allows practitioners to suspect the presence of IE. This diagnosis can be confirmed by meeting the criteria set out in the Modified Duke Criteria for Endocarditis. When using the Duke Criteria, there are three attainable results: rejected endocarditis, possible endocarditis, and definite endocarditis. These results depend on how many of the criteria the patient meets. The criteria are split into definitive pathological criteria, major criteria, and minor criteria. There are two definitive pathological criteria where if either of them are met, the diagnosis of IE is confirmed. The first pathological criteria is if a

specimen of the vegetation has been cultured and returns positive for bacteria, the diagnosis is confirmed. The second pathological criteria is if the vegetation or the abscess due to the vegetation is confirmed histologically to show active IE, the diagnosis is confirmed. If neither of these above pathological criteria are met, to confirm the diagnosis of IE would require a combination of two major criteria, one major and three minor criteria, or five minor criteria. In total, there are two major and five minor criteria. The two major criteria are the presence of endocardial involvement and a blood culture positive for IE. Endocardial involvement can include the presence of an abscess, the dehiscence of a prosthetic valve, or the presence of a mass on the valve that is confirmed by TEE or Transthoracic Echocardiogram (TTE). To have a blood culture positive for IE, there needs to have been two blood cultures drawn approximately 12 hours apart that both return positive for IE. If both of these major criteria are met, then your diagnosis of IE is confirmed. If none or only one of the criteria are met, you must move on to the minor criteria to confirm your diagnosis. The five minor criteria are: the presence of fever, a preexisting heart condition or intravenous drug use, the presence of vascular phenomena, the presence of specific immunological phenomena, and microbiological evidence. The presence of emboli, infarcts, or Janeway lesions, discussed above, fit into the domain of vascular phenomena. Roth spots, Osler nodes, or glomerulonephritis are examples of immunological phenomena that the Duke Criteria accept as a minor criteria. Finally, any microbiological evidence, such as only one positive blood culture, is sufficient to be considered as a minor criteria (L. M. Baddour, 2005; Durack, Lukes, & Bright, 1994; Li et al., 2000; Thuny, 2005).

Studies have been conducted that attempted to use serum biomarkers in order to predict outcomes for patients with IE. Biomarkers such as B-type natriuretic peptide (BNP), troponins, procalcitonin, and cystatin C have provided a foundation as a group of biomarkers that can potentially be used to determine a prognostic survival rate for patients diagnosed with IE. More research on these biomarkers needs to be conducted in order to introduce a reliable and accurate system for predicting the course of IE (Gucuk Ipek et al., 2015; Purcell et al., 2008; Shiue et al., 2010; Siciliano et al., 2014; Snipsøyr, Ludvigsen, Petersen, Wiggers, & Honoré, 2016)

Treatment of IE

With the diagnosis of IE comes a challenge: determining whether to treat the patient solely with antibiotics or a combination of antibiotics and surgery, most commonly valve replacement. This decision depends on many factors including the severity of infection, the risk of surgery, and the type of pathogen that has colonized the valve. Surgical intervention has shown to have positive outcomes in IE cases, but there is still debate about when to subject patients to a cardiac operation (Vikram, Buenconsejo, Hasbun, & Quagliarello, 2003). The location and size of the vegetation has played a major role in determining whether surgery or antibiotic therapy is recommended. Patients with mobile, large vegetations (>10mm) are more likely to develop emboli from the infection and should be operated on more urgently than patients with small, sessile vegetations (Tornos et al., 2005). Early surgery is also recommended for patients with preoperative cerebral emboli (Sorabella et al., 2015). The typical approach is to wait four weeks after the diagnosis of a septic brain embolus to allow for healing of the infarcted

tissue, but surgery less than 4 weeks after this diagnosis has not shown any significantly worse post-operative outcomes (Sorabella et al., 2015).

Traditionally, antibiotics are started immediately following the diagnosis of IE (Habib, 2006). Then, if surgery is indicated, the patient will begin preparation for a valve replacement surgery. The duration of antibiotic therapy before surgery is questioned, but there have been studies that state that the duration of antibiotic therapy before surgery has no effect on perioperative mortality or recurrence of IE (Chastre & Trouillet, 1995; d'Udekem, David, Feindel, Armstrong, & Sun, 1997; Delahaye, 2004; Olaison & Pettersson, 2002). If surgery is indicated, the procedure will replace the native valve with a prosthetic valve and the surgeon will ensure that the valve area is debrided of the infection. Common indications for surgery include presence of valvular abscess, valve dehiscence, severe valvular stenosis or regurgitation, and failure of initial antibiotic therapy (Anantha Narayanan et al., 2016).

The antibiotic therapy prescribed in IE depends on the type of pathogen that is present. The bacterial vegetation will consist of platelets, fibrin and bacteria that are attached to the valve which requires the therapy to contain a bactericidal element that can break through this material, regardless of the pathogen (Hoen, 2006). The antibiotics are most commonly administered intravenously for a period of four to six weeks to ensure that the patient receives the proper dosage. A Peripherally Inserted Central Catheter (PICC) can also be placed to facilitate the administration of the medication.

For native or prosthetic streptococcal IE, penicillin G and gentamicin are used in combination for a duration of four to six weeks (Hoen, 2006). Penicillin serves as the

antibacterial medication that will combat the infection and gentamicin serves as an aminoglycoside which inhibits protein synthesis (Graham, 2002; Öbrink-Hansen et al., 2017) . This combination is recommended to be followed for four weeks and the recommended dosage is 10-20 million units a day of penicillin G and 5-6mg/kg/day of gentamicin (Hoen, 2006; Öbrink-Hansen et al., 2017). In complicated cases of IE or in situations where the streptococci are resistant to penicillin, ceftriaxone, ampicillin, and amoxicillin can be used as substitutes.

For native valve staphylococcal IE that is oxacillin susceptible, 150mg/kg/day of oxacillin should be prescribed with gentamicin. This combination should be used together for approximately the first four days and then the oxacillin should be used alone for four to six weeks. If the staphylococcus is resistant to oxacillin, vancomycin is prescribed as an alternative. For prosthetic valve staphylococcal IE, a triple combination of vancomycin, rifampicin, and gentamicin is recommended (Larry M. Baddour et al., 2015; Hoen, 2006).

SPECIFIC AIMS

The purpose of this study is to analyze if surgical treatment of left-sided IE is associated with significantly lower perioperative (30 day) and 1 year post-operative outcomes compared to medical management after assessing for surgical risk and severity of pre-treatment infection. This study aims to determine the effect that various pathogens have on these outcomes and whether surgery should be considered earlier and more frequently in treatment of IE. Studies have shown that the duration of antibiotic therapy before surgery has no effect on perioperative mortality or recurrence of IE (Chastre & Trouillet, 1995; d'Udekem et al., 1997; Delahaye, 2004; Olaison & Pettersson, 2002) . Additionally, in patients with preoperative septic cerebral emboli, early operation for IE is not associated with significantly worse postoperative outcomes (Sorabella et al., 2015). These studies offer potential that surgical intervention may be more effective and can be used independently of traditional antibiotic therapy for treatment of IE. There has been no study that has examined surgically and medically treated patients with IE to determine which cohort of patients fared better at 30 days and 1 year post-treatment. This study will identify patients who have been diagnosed with left-sided valvular IE who have been treated medically and compare them to patients who underwent left-sided valve replacement surgery for IE.

METHODS

This is unpublished data and it is confidential. It is unfinalized.

We conducted a retrospective analysis of all patients diagnosed with IE at our institution, New York Presbyterian Hospital and Columbia University Medical Center, from April 1995 to December 2014. One thousand two hundred and ten (1210) patients were included in this initial analysis. These patients were then checked to ensure the fulfillment of the diagnosis of IE according to the Modified Duke Criteria. Any patient with possible IE or persistent bacteremia was excluded from the study. Next, the patients were stratified by infecting pathogen and three cohorts were created: one for Methicillin-Resistant Staphylococcus Aureus (MRSA), one for non-MRSA Staphylococci, and one for Streptococci. The three pathogens were selected due to their prevalence in the IE population. Within the three pathogen cohorts, another division was made that separated these patients into those managed medically for IE and those treated surgically. The medically managed cohort included patients who were treated with antibiotics for IE and the surgical cohort included patients who underwent valve replacement to treat their IE. These surgically and medically managed cohorts were used to determine which treatment method lead to superior perioperative and 1-year outcomes.

To assist with the comparison between the medical and surgical cohorts, Society of Thoracic Surgeon (STS) Scores for mortality were calculated for both groups. For the medical cohort, the “date of operation” was considered to be the date of initial definitive IE diagnosis and that was the date that was used to determine the 30 day and 1 year

window for post-treatment outcomes. Initial definitive IE diagnosis was defined as the first day when the patient exhibited a vegetation on a TTE or TEE and had positive blood cultures for an invading pathogen. Antibiotic therapy for possible IE may have been started prophylactically before definitive diagnosis but valvular surgery would not have been considered until there was the presence of a distinct vegetation and positive blood cultures.

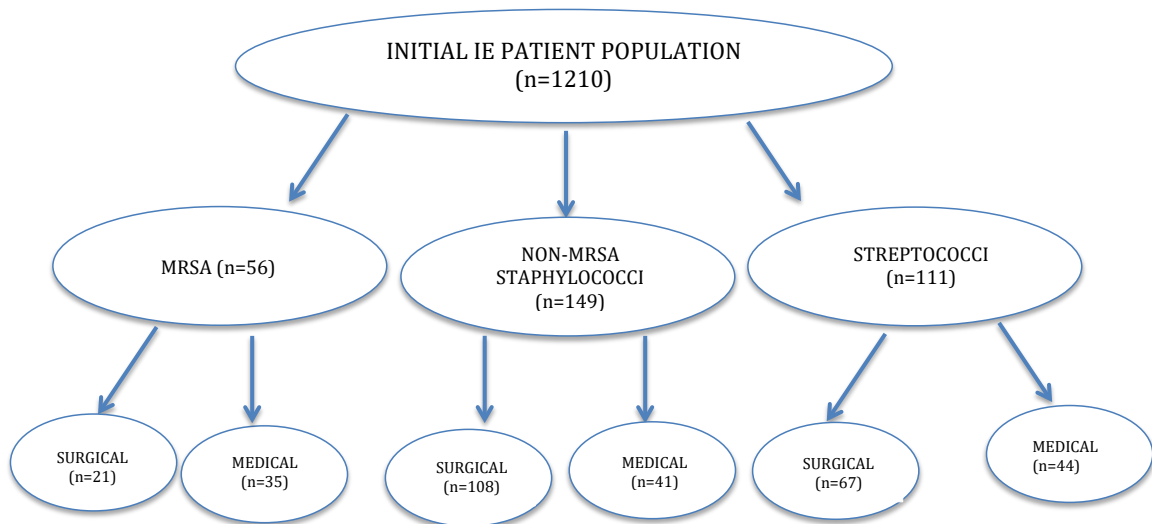


Figure 6: Breakdown of Included Patients. This image represents the amount of patients included in the data analysis portion of this study. It represents the breakdown and ultimate stratification of the variables that were included to determine if surgical treatment of IE is superior to medical management of IE.

Pathogen	Number of Patients	Percentage of Patients
Staphylococcus	416	34.38%
Streptococcus	242	20.00%
MRSA	142	11.74%
Enterococcus	93	7.69%
Candida	15	1.24%
Kliebsella	14	1.16%

Figure 7: Breakdown of Pathogens. This figure represents the most common pathogens found in our initial analysis of 1210 patients. This was the basis for selectively examining the outcomes of patients with Staphylococcus, Streptococcus, and MRSA IE.

Figure 7 represents the breakdown of the most common pathogens found in our institutions internal databases. Of the 1210 patients, 416 (34.38%) presented with Staphylococcus IE, 242 (20.00%) presented with Streptococcus IE, and 142 (11.74%) presented with MRSA IE. Because these three pathogens were the most prevalent in the population, we decided to examine left sided IE in patients with only these three bacteria. The total number of final patients that we used in our analysis is lower than the numbers represented above because the above numbers are patients with positive Staphylococcus blood cultures. They did not all satisfy the Duke Criteria for IE and were therefore excluded.

Variables included in the pre-operative characteristic section included basic demographic information, hypertension, diabetes mellitus (DM), congestive heart failure (CHF), cerebral vascular accident (CVA), end stage renal disease (ESRD), chronic

obstructive pulmonary disease (COPD), prior cardiac surgery, and arrhythmias. Data regarding the affected valve were collected as well. To determine severity of infection, data for fever, angina, and the presence of a valvular abscess were collected. Furthermore, all additional variables needed for calculation of STS Scores were collected and used in those calculations. If a patient was undergoing a procedure involving both a mitral valve replacement (MVR) and aortic valve replacement (AVR), the STS score for the AVR was used. If a patient underwent an aortic root replacement (ARR), the STS scores for an AVR were used.

Variables collected at for post-treatment outcomes at 30 days and 1 year were mortality, prosthetic valve dysfunction, septic shock, stroke, myocardial infarction (MI), embolic events, ESRD, and infection. All data were collected retrospectively from electronic medical records.

To determine significance between the medical and surgical cohorts, T-tests were run to determine the p values. P values less than 0.05 were considered statistically significant.

A Cox Regression analysis was also performed to control for pre-therapy comorbidities and demographics and predict the likelihood of mortality based on the patient's preoperative patient characteristics. Hazard ratios and 95% confidence intervals were used to determine the direction and significance of each of the comorbidities. Variables used for the Cox regression were sex, age, prior cardiac surgery, CHF, HTN, CHF, DM, CVA, MI, AFIB, ESRD, COPD, STS score, Abscess, Fever, and Angina. 4

regressions were run to determine the hazard ratios for 30 day and 1 year mortality for both the surgical and medical cohort.

Finally, a Kaplan Meier Analysis was conducted to graph the survival of the surgical and medical patients at both 30 days and 1 year. This visual representation of the mortality rates of this study will confirm the significance in mortality, if any, between the cohorts.

RESULTS

Surgical patient data is reflected in Figure 8. One hundred ninety six (196) surgical patients were identified and their mean age was 58.07. One hundred twenty six (126) patients (63.64%) were males and seventy one (70) patients were females (36.36%). 49.49% of patients are White, 10.71% are Hispanic or Latino, 10.20 % are African American, and 38.78% are unknown. Sixty seven (67) patients had prior cardiac surgery and fifty one (51) presented with prosthetic valve endocarditis. 55.1% of the surgical patients had Staphylococcus IE, 34.18% presented with Streptococcus IE, and 10.7% presented with MRSA IE.

Medical patient data is presented in Table 9. One hundred and twenty (120) patients treated medically for IE were identified. Sixty seven (67) patients (55.83%) are male and fifty three (53) patients (45.45%) are female. 45.45% of patients are White, 14.05% are African American, 38.85% are unknown and 22.31% are Hispanic or Latino. Thirty four (34) patients had prior cardiac surgery and twenty one (21) presented with prosthetic valve endocarditis. 34.16% of the medical patients had Staphylococcus IE, 36.67% presented with Streptococcus IE, and 29.16% presented with MRSA IE.

SURGICAL	Overall (n=196)	Staph (n=108)	MRSA(n=21)	Strep(n=67)
Age	58.07	58.67	61.03	56.19
Male, n (%)	126 (63.64)	63 (58.33)	15 (71.43)	48 (71.64)
Female, n (%)	70 (36.36)	45 (41.67)	6 (28.57)	19 (28.36)
White, n (%)	97 (49.49)	42 (38.89)	12 (57.14)	43 (64.18)
Unknown, n (%)	76 (38.78)	49 (45.37)	7 (34.34)	20 (29.86)
Black African American, n (%)	20 (10.20)	14 (12.96)	2 (9.52)	4 (5.97)
Hispanic or Latino, n (%)	21 (10.71)	12 (11.11)	3 (14.29)	6 (8.96)
Co-Morbidities				
Hypertension, n (%)	128 (65.31)	73 (67.59)	13 (61.90)	42 (62.69)
Diabetes, n (%)	48 (24.49)	30 (27.78)	8 (38.10)	10 (14.93)
CHF, n (%)	84 (42.86)	44 (40.74)	14 (66.67)	26 (38.81)
CVA, n (%)	55 (28.06)	33 (30.56)	5 (23.81)	17 (25.37)
ESRD, n (%)	27 (13.78)	20 (18.52)	6 (28.57)	1 (1.49)
COPD, n (%)	25 (12.76)	16 (14.81)	2 (9.52)	7 (10.45)
Arrhythmia, n (%)	39 (19.90)	26 (24.07)	3 (14.29)	10 (14.93)
Affected Valve				
Aortic, n (%)	109 (55.61)	59 (54.63)	9 (42.86)	41 (61.19)
Mitral, n (%)	135 (68.88)	70 (64.81)	16 (76.19)	49 (73.13)
Tricuspid, n (%)	16 (8.16)	10 (9.26)	3 (14.29)	3 (4.48)
Pre-Op Severity				
Fever, n (%)	135 (68.88)	71 (65.74)	15 (71.43)	49 (73.13)
Angina, n (%)	27 (13.78)	15 (13.89)	5 (23.81)	7 (10.45)
Abscess, n (%)	66 (33.67)	42 (38.89)	10 (47.62)	14 (20.90)
Reoperation				
Prior Cardiac Surgeries, n (%)	67 (34.18)	48 (44.44)	5 (23.81)	17 (25.37)
Average STS Score	6.73	7.97	9.20	4.18
30 Day Post-Op Outcomes				
Mortality, n (%)	15 (7.65)	10 (9.26)	1 (4.76)	4 (5.97)
Prosthetic Valve Dysfunction, n (%)	2 (1.02)	2 (1.85)	0 (0.0)	0 (0.0)
Septic Shock, n (%)	30 (15.31)	17 (15.74)	3 (14.29)	10 (14.93)

MI, n (%)	29 (14.80)	13 (12.04)	7 (33.33)	9 (13.43)
Stroke, n (%)	10 (5.10)	5 (4.63)	1 (4.76)	4 (5.97)
Embolic Events, n (%)	32 (16.33)	18 (16.67)	2 (9.52)	12 (17.91)
ARF/ESRD, n (%)	40 (20.41)	25 (23.15)	6 (28.57)	9 (13.43)
Infection, n (%)	39 (19.90)	24 (22.22)	7 (33.33)	8 (11.94)
1 Year Post-Op Outcomes				
Mortality, n (%)	34 (17.35)	23 (21.30)	6 (28.57)	5 (7.46)
Prosthetic Valve Dysfunction, n (%)	10 (5.10)	6 (5.56)	2 (9.52)	2 (2.99)
Septic Shock, n (%)	34 (17.35)	20 (18.52)	4 (19.05)	10 (14.93)
MI, n (%)	32 (16.33)	16 (14.81)	7 (33.33)	9 (13.43)

Figure 8: Surgical Patient Data. The demographic, pre-operative, and post-operative outcomes collected for the surgical patients are represented in this figure. The total number of patients as well as the percentages in each category are reflected in this figure.

MEDICAL	Overall (n=120)	Staph (n=41)	MRSA (n=35)	Strep (n=44)
Age	65.67	63.80	68.34	65.29
Male, n (%)	67 (55.83)	20 (48.78)	15 (42.86)	32 (72.73)
Female, n (%)	53 (44.17)	21 (51.22)	20 (57.14)	12 (27.27)
White, n (%)	55 (45.45)	20 (46.51)	15 (42.86)	20 (45.45)
Unknown, n (%)	47 (38.85)	16 (38.21)	13 (37.14)	18 (40.91)
Black African American, n (%)	17 (14.05)	5 (11.63)	7 (20.00)	5 (11.36)
Hispanic or Latino, n (%)	27 (22.31)	11 (25.58)	5 (14.29)	11 (25.00)
Co-Morbidities				
Hypertension, n (%)	69 (57.50)	25 (60.98)	24 (68.57)	20 (45.45)
Diabetes, n (%)	46 (38.33)	18 (43.90)	17 (48.57)	11 (25.00)
CHF, n (%)	32 (26.67)	13 (31.71)	10 (28.57)	9 (20.45)
CVA, n (%)	16 (13.33)	3 (7.32)	7 (20.00)	6 (13.64)
ESRD, n (%)	18 (15.00)	8 (19.51)	9 (25.71)	1 (2.27)
COPD, n (%)	12 (10.00)	4 (9.76)	6 (17.14)	2 (4.55)
Arrhythmia, n (%)	29 (24.17)	6 (14.63)	11 (31.43)	12 (27.27)
Affected Valve				
Aortic, n (%)	52 (43.33)	16 (39.02)	12 (34.29)	24 (54.55)
Mitral, n (%)	69 (57.50)	25 (60.98)	23 (65.71)	21 (47.73)
Pre-Op Severity				
Fever, n (%)	63 (52.50)	20 (48.78)	16 (45.71)	27 (61.36)
Angina, n (%)	3 (2.50)	0 (0.00)	0 (0.0)	3 (6.82)
Abscess, n (%)	8 (6.67)	4 (9.76)	2 (5.71)	2 (4.55)
Reoperation				
Prior Cardiac Surgeries, n (%)	34 (28.33)	8 (19.51)	7 (20.00)	19 (43.18)
Average STS Score	9.01	11.10	11.14	5.485
30 Day Post-Op Outcomes				
Mortality, n (%)	35 (29.17)	14 (34.15)	16 (45.71)	5 (11.36)
Prosthetic Valve Dysfunction, n (%)	0 (0.00)	0 (0.00)	0 (0.0)	0 (0.0)
Septic Shock, n (%)	14 (11.67)	3 (7.32)	8 (22.86)	3 (6.82)

MI, n (%)	4 (3.33)	2 (4.88)	1 (2.86)	1 (2.27)
Stroke, n (%)	11 (9.17)	4 (9.76)	4 (11.43)	3 (6.82)
Embolic Events, n (%)	23 (19.17)	9 (21.95)	7 (20.00)	7 (15.91)
ARF/ESRD, n (%)	4 (3.33)	0 (0.00)	4 (11.43)	0 (0.0)
Infection, n (%)	2 (1.67)	2 (4.88)	0 (0.0)	0 (0.0)
1 Year Post-Op Outcomes				
Mortality, n (%)	56 (46.67)	21 (51.22)	26 (74.29)	9 (20.45)
Prosthetic Valve Dysfunction, n (%)	0 (0.00)	0 (0.00)	0 (0.0)	0 (0.0)
Septic Shock, n (%)	17 (14.17)	3 (7.32)	11 (31.43)	3 (6.82)
MI, n (%)	4 (3.33)	2 (4.88)	1 (2.86)	1 (2.27)
Stroke, n (%)	13 (10.83)	4 (9.76)	5 (14.29)	4 (9.09)
Embolic Events, n (%)	24 (20.00)	9 (21.95)	7 (20.00)	8 (18.18)
ARF/ESRD, n (%)	6 (5.00)	0 (0.00)	5 (14.29)	1 (2.27)
Infection, n (%)	8 (6.67)	6 (14.63)	0 (0.0)	2 (4.55)

Figure 9: Medical Patient Data. The demographic, pre-operative, and post-operative outcomes collected for the medical patients are represented in this figure. The total number of patients as well as the percentages in each category are reflected in this figure.

The overall comparison for of surgical and medical patients is presented in Table 10. T tests were conducted to determine if there was a significant difference between the two cohorts. The medical patients had a significantly higher preoperative prevalence of diabetes ($p=0.005$) while the surgical patients had higher preoperative instances of CHF ($p=0.001$) and CVA ($p=0.0005$). The surgical patients also presented with a higher severity of infection and had significantly higher rates of preoperative fever ($p=0.002$), angina ($p=0.00004$), and valvular abscess ($p<0.5$). Overall, the STS score for the medical patients was an average of 9.01 which was significantly higher than the 6.73 of surgical patients ($p=0.017$). Surgical patients also had a higher percentage of prior cardiac surgeries, but this number was not significantly different that the medical patients.

Postoperatively, medical patients exhibited a significantly higher rate of mortality at both 30 days and 1 year post-op ($p<0.05$). However, surgical patients presented with significantly higher rates of MI, ARF, and recurrence of infection at both 30 days and 1 year ($p<0.05$).

	Surgical (n=196)	Medical (n=120)	P value
Age	58.07	65.67	
Male, n (%)	126 (63.64)	67 (55.83)	
Female, n (%)	70 (36.36)	53 (44.17)	
Co-Morbidities			
Hypertension, n (%)	128 (65.31)	69 (57.50)	0.085
Diabetes, n (%)	48 (24.49)	46 (38.33)	0.005
CHF, n (%)	84 (42.86)	32 (26.67)	0.001
CVA, n (%)	55 (28.06)	16 (13.33)	0.0005
ESRD, n (%)	27 (13.78)	18 (15.00)	0.382
COPD, n (%)	25 (12.76)	12 (10.00)	0.225
Arrhythmia, n (%)	39 (19.90)	29 (24.17)	0.190
Affected Valve			
Aortic, n (%)	109 (55.61)	52 (43.33)	
Mitral, n (%)	135 (68.88)	69 (57.50)	
Tricuspid, n (%)	16 (8.16)		
Pre-Op Severity			
Fever, n (%)	135 (68.88)	63 (52.50)	0.002
Angina, n (%)	27 (13.78)	3 (2.50)	0.00004
Abscess, n (%)	66 (33.67)	8 (6.67)	0.0000000006
Reoperation			
Prior Cardiac Surgeries, n (%)	67 (34.18)	34 (28.33)	0.137
Average STS Score	6.73	9.01	0.017
30 Day Post-Op Outcomes			
Mortality, n (%)	15 (7.65)	35 (29.17)	0.000002
Prosthetic Valve Dysfunction, n (%)	2 (1.02)	0 (0.00)	0.079
Septic Shock, n (%)	30 (15.31)	14 (11.67)	0.177
MI, n (%)	29 (14.80)	4 (3.33)	0.00009
Stroke, n (%)	10 (5.10)	11 (9.17)	0.094
Embolic Events, n (%)	32 (16.33)	23 (19.17)	0.263
ARF/ESRD, n (%)	40 (20.41)	4 (3.33)	0.0000002
Infection, n (%)	39 (19.90)	2 (1.67)	0.00000005
1 Year Post-Op Outcomes			
Mortality, n (%)	34 (17.35)	56 (46.67)	0.00000005
Prosthetic Valve Dysfunction, n (%)	10 (5.10)	0 (0.00)	0.0007
Septic Shock, n (%)	34 (17.35)	17 (14.17)	0.224

MI, n (%)	32 (16.33)	4 (3.33)	0.00002
Stroke, n (%)	30 (15.31)	13 (10.83)	0.122
Embolic Events, n (%)	39 (19.90)	24 (20.00)	0.491
ARF/ESRD, n (%)	46 (23.47)	6 (5.00)	0.000003
Infection, n (%)	55 (28.06)	8 (6.67)	0.0000005

Figure 10: Surgical vs. Medical Patient Data Comparison. The demographic, pre-operative, and post-operative outcomes collected for the medical patients are represented in this figure. The total number of patients as well as the percentages in each category are reflected in this figure.

The surgical and medical cohorts were then further subdivided by invading pathogen to analyze the pre and post treatment comorbidities and outcomes. The Streptococcus subdivision yielded sixty seven (67) surgical patients with an average age of 56.19 and forty four (44) medical patients with an average age of 65.29. Medical patients exhibited significantly higher rates of preoperative arrhythmia and surgical patients exhibited higher rates of preoperative hypertension, CHF, and abscess ($p < 0.05$). Although the average STS score was higher for medical patients than surgical patients, it was not statistically significant. At 30 days, there was no statistically significant difference in mortality, however, there was a much higher rate of MI in the surgical cohort ($p = 0.010$). At 1 year post-treatment, medical patients had a significantly higher mortality rate ($p = 0.032$) despite surgical patients exhibited higher rates of MI, ESRD, and recurrence of infection.

	Strep Surgical (n=67)	Strep Medical (n=44)	P value
Age	56.19	65.29	
Male, n (%)	48 (71.64)	32 (72.73)	
Female, n (%)	19 (28.36)	12 (27.27)	
Co-Morbidities			
Hypertension, n (%)	42 (62.69)	20 (45.45)	0.039
Diabetes, n (%)	10 (14.93)	11 (25.00)	0.103
CHF, n (%)	26 (38.81)	9 (20.45)	0.018
CVA, n (%)	17 (25.37)	6 (13.64)	0.060
ESRD, n (%)	1 (1.49)	1 (2.27)	0.387
COPD, n (%)	7 (10.45)	2 (4.55)	0.117
Arrhythmia, n (%)	10 (14.93)	12 (27.27)	0.040
Affected Valve			
Aortic, n (%)	41 (61.19)	24 (54.55)	
Mitral, n (%)	49 (73.13)	21 (47.73)	
Tricuspid, n (%)	3 (4.48)		
Pre-Op Severity			
Fever, n (%)	49 (73.13)	27 (61.36)	0.102
Angina, n (%)	7 (10.45)	3 (6.82)	0.251
Abscess, n (%)	14 (20.90)	2 (4.55)	0.003
Reoperation			
Prior Cardiac Surgeries, n (%)	17 (25.37)	19 (43.18)	0.135
Average STS Score	4.18	5.485	0.06
30 Day Post-Op Outcomes			
Mortality, n (%)	4 (5.97)	5 (11.36)	0.171
Prosthetic Valve Dysfunction, n (%)	0 (0.0)	0 (0.0)	
Septic Shock, n (%)	10 (14.93)	3 (6.82)	0.083
MI, n (%)	9 (13.43)	1 (2.27)	0.010
Stroke, n (%)	4 (5.97)	3 (6.82)	0.430
Embolic Events, n (%)	12 (17.91)	7 (15.91)	0.392
ARF/ESRD, n (%)	9 (13.43)	0 (0.0)	0.001
Infection, n (%)	8 (11.94)	0 (0.0)	0.002
1 Year Post-Op Outcomes			
Mortality, n (%)	5 (7.46)	9 (20.45)	0.032
Prosthetic Valve Dysfunction, n (%)	2 (2.99)	0 (0.0)	0.079

Septic Shock, n (%)	10 (14.93)	3 (6.82)	0.084
MI, n (%)	9 (13.43)	1 (2.27)	0.010
Stroke, n (%)	8 (11.94)	4 (9.09)	0.315
Embolic Events, n (%)	13 (19.40)	8 (18.18)	0.437
ARF/ESRD, n (%)	10 (14.93)	1 (2.27)	0.006
Infection, n (%)	10 (20.41)	2 (4.55)	0.029

Figure 11: Streptococci Surgical vs. Medical Patient Data. The demographic, pre-operative, and post-operative outcomes collected for the Streptococci surgical and medical patients are represented in this figure. The total number of patients as well as the percentages in each category are reflected in this figure.

The Staphylococcus subdivision yielded one hundred eight (108) surgical patients with an average age of 58.67 and forty one (41) medical patients with an average age of 63.80. Medical patients exhibited significantly higher rates of preoperative diabetes ($p=0.038$) and surgical patients exhibited higher rates of preoperative CVA ($p=0.0001$), prior cardiac surgery ($p=0.001$), fever ($p=0.034$), angina ($p<0.05$) and abscess ($p<0.05$). At 30 days, medical patients had a significantly higher rate of mortality ($p=0.001$) although surgical patient had significantly higher rates of ESRD ($p<0.05$) and recurrence of infection ($p<0.05$). At 1 year, the disparities increase significantly. Medical patients had significantly higher rates of mortality ($p<0.05$) but surgical patients experienced higher rates of septic shock, MI, ESRD, and recurrence of infection ($p<0.05$).

	Staph (n=108)	Staph Medical (n=41)	P value
Age	58.67	63.80	
Male, n (%)	63 (58.33)	20 (48.78)	
Female, n (%)	45 (41.67)	21 (51.22)	
Co-Morbidities			
Hypertension, n (%)	73 (67.59)	25 (60.98)	0.159
Diabetes, n (%)	30 (27.78)	18 (43.90)	0.038
CHF, n (%)	44 (40.74)	13 (31.71)	0.153
CVA, n (%)	33 (30.56)	3 (7.32)	0.0001
ESRD, n (%)	20 (18.52)	8 (19.51)	0.446
COPD, n (%)	16 (14.81)	4 (9.76)	0.193
Arrhythmia, n (%)	26 (24.07)	6 (14.63)	0.089
Affected Valve			
Aortic, n (%)	59 (54.63)	16 (39.02)	
Mitral, n (%)	70 (64.81)	25 (60.98)	
Tricuspid, n (%)	10 (9.26)		
Pre-Op Severity			
Fever, n (%)	71 (65.74)	20 (48.78)	0.034
Angina, n (%)	15 (13.89)	0 (0.00)	0.00003
Abscess, n (%)	42 (38.89)	4 (9.76)	0.00001
Reoperation			
Prior Cardiac Surgeries, n (%)	48 (44.44)	8 (19.51)	0.001
Average STS Score	7.97	11.10	0.078
30 Day Post-Op Outcomes			
Mortality, n (%)	10 (9.26)	14 (34.15)	0.001
Prosthetic Valve Dysfunction, n (%)	2 (1.85)	0 (0.00)	0.079
Septic Shock, n (%)	17 (15.74)	3 (7.32)	0.062
MI, n (%)	13 (12.04)	2 (4.88)	0.063
Stroke, n (%)	5 (4.63)	4 (9.76)	0.160
Embolic Events, n (%)	18 (16.67)	9 (21.95)	0.240
ARF/ESRD, n (%)	25 (23.15)	0 (0.00)	0.0000001
Infection, n (%)	24 (22.22)	2 (4.88)	0.0006
1 Year Post-Op Outcomes			
Mortality, n (%)	23 (21.30)	21 (51.22)	0.0005
Prosthetic Valve Dysfunction, n (%)	6 (5.56)	0 (0.00)	0.006
Septic Shock, n (%)	20 (18.52)	3 (7.32)	0.023

MI, n (%)	16 (14.81)	2 (4.88)	0.021
Stroke, n (%)	17 (15.74)	4 (9.76)	0.155
Embolic Events, n (%)	22 (20.37)	9 (21.95)	0.418
ARF/ESRD, n (%)	29 (26.85)	0 (0.00)	0.0000004
Infection, n (%)	36 (33.33)	6 (14.63)	0.0055

Figure 12: Staphylococci Surgical vs. Medical Patient Data. The demographic, pre-operative, and post-operative outcomes collected for the Streptococci surgical and medical patients are represented in this figure. The total number of patients as well as the percentages in each category are reflected in this figure.

The MRSA subdivision yielded twenty one (21) surgical patients with an average age of 61.03 and thirty five (35) medical patients with an average age of 68.34. Surgical patients exhibited significantly higher rates of preoperative CHF, fever, angina and abscess. At both 30 days and 1 year, medical patients had significantly higher rates of mortality ($p < 0.05$) and surgical patients had significantly higher rates of recurrence of infection ($p < 0.05$).

	MRSA (n=21)	MRSA Medical (n=35)	P value
Age	61.03	68.34	
Male, n (%)	15 (71.43)	15 (42.86)	
Female, n (%)	6 (28.57)	20 (57.14)	
Co-Morbidities			
Hypertension, n (%)	13 (61.90)	24 (68.57)	0.438
Diabetes, n (%)	8 (38.10)	17 (48.57)	0.186
CHF, n (%)	14 (66.67)	10 (28.57)	0.005
CVA, n (%)	5 (23.81)	7 (20.00)	0.310
ESRD, n (%)	6 (28.57)	9 (25.71)	0.315
COPD, n (%)	2 (9.52)	6 (17.14)	0.187
Arrhythmia, n (%)	3 (14.29)	11 (31.43)	0.055
Affected Valve			
Aortic, n (%)	9 (42.86)	12 (34.29)	
Mitral, n (%)	16 (76.19)	23 (65.71)	
Tricuspid, n (%)	3 (14.29)		
Pre-Op Severity			
Fever, n (%)	15 (71.43)	16 (45.71)	0.048
Angina, n (%)	5 (23.81)	0 (0.0)	0.005
Abscess, n (%)	10 (47.62)	2 (5.71)	0.001
Reoperation			
Prior Cardiac Surgeries, n (%)	5 (23.81)	7 (20.00)	0.063
Average STS Score	9.20	11.14	0.118
30 Day Post-Op Outcomes			
Mortality, n (%)	1 (4.76)	16 (45.71)	0.0004
Prosthetic Valve Dysfunction, n (%)	0 (0.0)	0 (0.0)	
Septic Shock, n (%)	3 (14.29)	8 (22.86)	0.189
MI, n (%)	7 (33.33)	1 (2.86)	0.006
Stroke, n (%)	1 (4.76)	4 (11.43)	0.168
Embolic Events, n (%)	2 (9.52)	7 (20.00)	0.122
ARF/ESRD, n (%)	6 (28.57)	4 (11.43)	0.082
Infection, n (%)	7 (33.33)	0 (0.0)	0.003
1 Year Post-Op Outcomes			
Mortality, n (%)	6 (28.57)	26 (74.29)	0.0002

Prosthetic Valve Dysfunction, n (%)	2 (9.52)	0 (0.0)	0.081
Septic Shock, n (%)	4 (19.05)	11 (31.43)	0.129
MI, n (%)	7 (33.33)	1 (2.86)	0.006
Stroke, n (%)	5 (23.81)	5 (14.29)	0.222
Embolic Events, n (%)	4 (19.05)	7 (20.00)	0.434
ARF/ESRD, n (%)	7 (33.33)	5 (14.29)	0.073
Infection, n (%)	9 (42.86)	0 (0.0)	0.0005

Figure 13: MRSA Surgical vs. Medical Patient Data. The demographic, pre-operative, and post-operative outcomes collected for the MRSA surgical and medical patients are represented in this figure. The total number of patients as well as the percentages in each category are reflected in this figure.

Procedure	Number of Patients, (%)
MVR	65, (33.16)
AVR	48, (24.49)
AVR/MVR	30, (15.31)
ARR	12, (6.12)
MVr	11, (5.61)
MVR/CABG	10, (5.10)
AVR/CABG	6, (3.06)

Figure 14: Surgical Procedures. The most popular procedures that were performed for IE. Other procedures also included Aortic Valve Repair (AVr), AVR/MVR/Coronary Artery Bypass Graft (CABG), and ARR/CABG.

In Figure 14, the most common surgical interventions are listed. Single or multiple valve replacement procedures were more prevalent than valve repair procedures, aortic root replacements, and procedures involving CABG. 33.16% of patients received

an MVR, 24.49% of patients received and AVR and 15.31% of patients received both an MVR and AVR.

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Sex	-.416	.591	.495	1	.482	.660	.207	2.102
Age	.036	.026	1.912	1	.167	1.036	.985	1.090
PriorSurgery	.164	.608	.073	1	.788	1.178	.358	3.876
CHF	-.246	.587	.176	1	.674	.782	.248	2.468
HTN	-.760	.676	1.261	1	.261	.468	.124	1.761
DM	.732	.637	1.318	1	.251	2.078	.596	7.248
CVA	.015	.634	.001	1	.981	1.015	.293	3.514
MI	.917	.659	1.935	1	.164	2.502	.687	9.110
AFIB	.229	.685	.111	1	.739	1.257	.328	4.808
ESRD	1.064	.888	1.436	1	.231	2.899	.508	16.527
COPD	.025	.810	.001	1	.976	1.025	.210	5.012
STS	-.016	.046	.124	1	.724	.984	.899	1.077
Abscess	-.751	.695	1.170	1	.279	.472	.121	1.841
Fever	-.061	.639	.009	1	.924	.941	.269	3.292
Angina	.623	.652	.915	1	.339	1.865	.520	6.690

Figure 15: 30 Day Surgical Cox Regression. A Cox Regression Analysis was conducted to control for pre-therapy comorbidities and demographics and predict the likelihood of mortality based on the patient’s preoperative patient characteristics. The results for the surgical cohort of patients at 30 Days is represented here.

Figure 15 displays the results of the Cox Regression analysis performed at 30 Days for the patients in the surgical cohort. There was no variable that returned significant in this analysis.

Figure 16 displays the results of the Cox Regression analysis performed at 1 year for the patients in the surgical cohort. Age (p=0.049), HTN (p=0.016), and ESRD (p=0.019) proved to be significant predictors of mortality. As age increases by 1 year (HR: 1.033, 1.000-1.066 95% CI, p=0.049), there is an increase in risk in experiencing mortality. Similarly, as patients are diagnosed with ESRD (HR: 3.561; 1.235-10.267 95%

CI, p=0.019), the risk of mortality from IE increases. Conversely, as patients are diagnosed with HTN (HR: 0.318, .126-.805 95% CI, p=0.016) the risk of mortality from IE decreases at 1 year.

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Sex	.045	.402	.013	1	.910	1.046	.476	2.300
Age	.032	.016	3.859	1	.049	1.033	1.000	1.066
PriorSurgery	.313	.399	.616	1	.433	1.367	.626	2.986
CHF	.526	.381	1.901	1	.168	1.692	.801	3.572
HTN	-1.144	.473	5.846	1	.016	.318	.126	.805
DM	.650	.423	2.362	1	.124	1.916	.836	4.390
CVA	.021	.405	.003	1	.958	1.022	.462	2.259
MI	.308	.464	.439	1	.508	1.360	.547	3.380
AFIB	.050	.473	.011	1	.917	1.051	.415	2.658
ESRD	1.270	.540	5.529	1	.019	3.561	1.235	10.267
COPD	.156	.511	.093	1	.761	1.168	.429	3.181
STS	.009	.026	.118	1	.732	1.009	.959	1.061
Abscess	-.301	.406	.551	1	.458	.740	.334	1.639
Fever	.360	.436	.683	1	.408	1.434	.610	3.368
Angina	.288	.449	.412	1	.521	1.334	.553	3.219

Figure 16: 1 Year Surgical Cox Regression. A Cox Regression Analysis was conducted to control for pre-therapy comorbidities and demographics and predict the likelihood of mortality based on the patient’s preoperative patient characteristics. The results for the surgical cohort of patients at 1 year is represented here.

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Sex	-.033	.375	.008	1	.930	.967	.464	2.018
Age	.016	.015	1.072	1	.301	1.016	.986	1.046
PriorSurgery	-.745	.554	1.804	1	.179	.475	.160	1.408
CHF	-.184	.484	.144	1	.705	.832	.322	2.151
HTN	-.496	.466	1.135	1	.287	.609	.244	1.517
DM	.344	.437	.618	1	.432	1.411	.598	3.325
CVA	.607	.492	1.520	1	.218	1.835	.699	4.815
MI	.320	.655	.239	1	.625	1.378	.381	4.977
AFIB	.628	.496	1.604	1	.205	1.873	.709	4.948
ESRD	.073	.629	.013	1	.908	1.076	.314	3.691
COPD	-.935	.769	1.479	1	.224	.393	.087	1.771
STS	.010	.027	.130	1	.719	1.010	.957	1.065
Abscess	1.148	.524	4.792	1	.029	3.151	1.128	8.806
Fever	-.532	.373	2.032	1	.154	.587	.283	1.221
Angina	-12.158	485.450	.001	1	.980	.000	.000	.

Figure 17: 30 Day Medical Cox Regression. A Cox Regression Analysis was conducted to control for pre-therapy comorbidities and demographics and predict the likelihood of mortality based on the patient’s preoperative patient characteristics. The results for the medical cohort of patients at 30 Days is represented here.

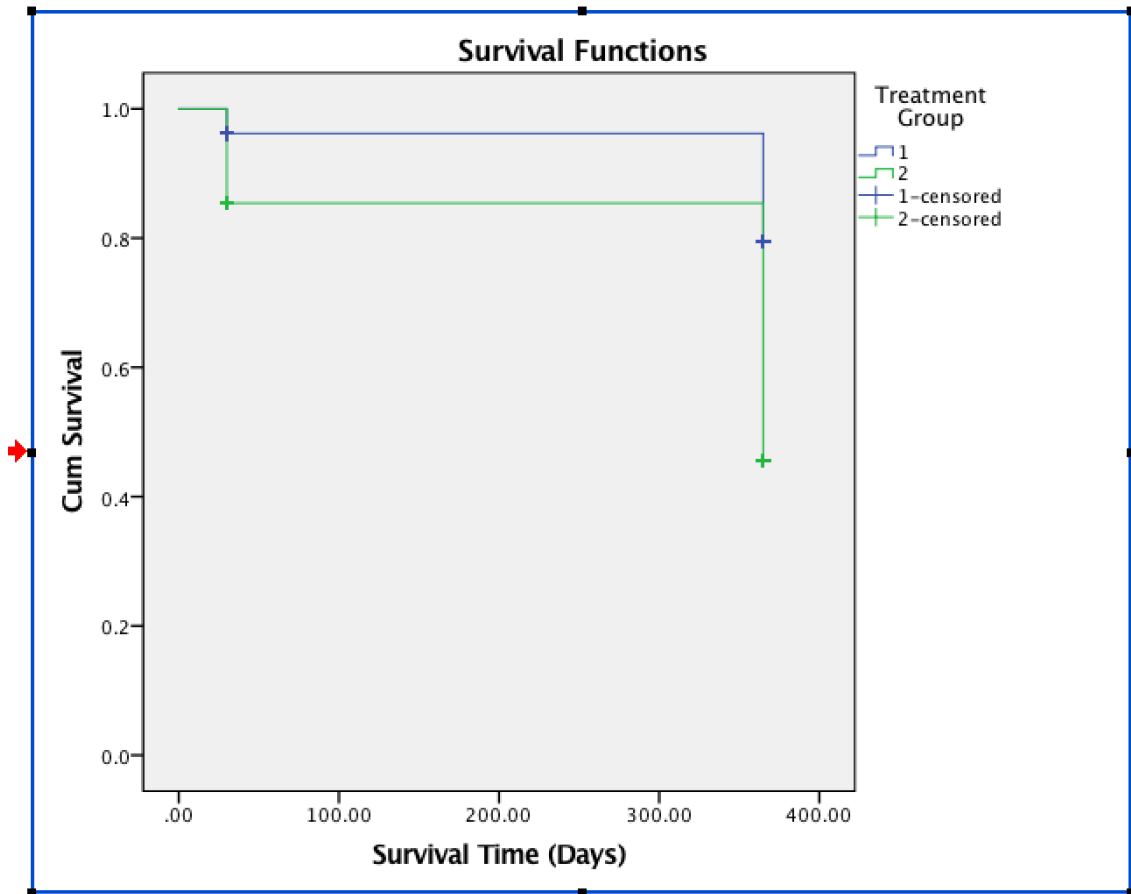
Figure 17 displays the results of the Cox Regression analysis performed at 30 Days for the patients in the medical cohort. The only significant result from this analysis was that the presence of valvular abscess (HR: 3.151, 1.128-8.806 95% CI, p=0.029) increases the risk of mortality at 30 Days. All other variables had no effect on mortality at 30 Days in the medical patients.

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Sex	-.144	.295	.240	1	.625	.866	.486	1.543
Age	.006	.011	.293	1	.588	1.006	.984	1.029
PriorSurgery	-.444	.394	1.269	1	.260	.642	.296	1.389
CHF	-.026	.365	.005	1	.943	.974	.476	1.992
HTN	-.442	.368	1.441	1	.230	.643	.312	1.323
DM	.422	.335	1.593	1	.207	1.526	.792	2.940
CVA	-.024	.445	.003	1	.957	.976	.408	2.336
MI	-.249	.612	.166	1	.684	.779	.235	2.585
AFIB	.399	.381	1.094	1	.296	1.490	.706	3.148
ESRD	.193	.469	.169	1	.681	1.213	.483	3.043
COPD	-.594	.555	1.143	1	.285	.552	.186	1.640
STS	.018	.020	.799	1	.372	1.018	.979	1.058
Abscess	.636	.453	1.971	1	.160	1.889	.777	4.588
Fever	-.661	.297	4.949	1	.026	.516	.288	.924
Angina	-.285	1.079	.070	1	.792	.752	.091	6.234

Figure 18: 1 Year Medical Cox Regression. A Cox Regression Analysis was conducted to control for pre-therapy comorbidities and demographics and predict the likelihood of mortality based on the patient’s preoperative patient characteristics. The results for the medical cohort of patients at 1 Year is represented here.

Figure 18 displays the results of the Cox Regression analysis performed at 1 Year for the patients in the medical cohort. The only significant result from this analysis was that the presence of fever (HR: 0.516, 0.288-0.924 95% CI, p=0.026) decreases the risk of mortality at 1 year. All other variables had no effect on mortality at 30 Days in the medical patients.



Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	54.907	1	.000

Test of equality of survival distributions for the different levels of Treatment Group.

Figure 19: Kaplan Meier Curve for 30 Day and 1 Year Comparisons. A Kaplan Meier Analysis was conducted to graph the survival of the surgical and medical patients at both 30 days and 1 year

Figure 19 graphically portrays the mortality amongst the surgical and medical cohorts at both 30 days and 1 year. The p value is <0.05 for this graph and confirms the significance that was first calculated in the T tests.

DISCUSSION

Staphylococcus, MRSA, and Streptococcus are the major causative organisms of IE. IE is a serious disease with a complicated prognosis and involves a clinical course that offers opportunities for medical management and surgical intervention. Clinicians weigh the severity of the infection and the surgical risk when deciding which option is the best fit for their patients. Known outcomes of medical management and surgical intervention greatly assist the clinician in making their ultimate decision. In this study, perioperative and 1 year mortality for treatment of IE was significantly higher in the medical cohort than the surgical population once all 3 subgroups were analyzed together. When analyzed separately, the Staphylococcus and MRSA group continued to show that medical management leads to significantly higher mortality rates at 30 days and 1 year while the Streptococcus group presented significance only at 1 year.

IE is a very rare disease that affects less than 1% of the population, but once contracted, it holds a 1-year mortality rate of 40%. It is thus important to gather data that examine and compare patients treated medically and surgically in order to determine the extent of post-treatment complications.

As expected, the surgical cohort displayed significantly higher preoperative comorbidities than the medical cohort. Significantly higher rates of CHF and preoperative CVA were observed. Though not significant, the surgical cohort had higher rates of COPD, hypertension, and prior cardiac surgery as well. Furthermore, surgical patients showed significantly higher rates of preoperative fever, angina, and abscess. The

combination of these factors places the surgical patients in a more severe category of IE infection than the medical patients. Despite evidence that surgical patients had a more severe case of infection, they had a significantly lower STS score. This can be attributed to the higher overall age of the medical patients and the higher proportion of females in the medical cohort- which both contribute to higher STS scores for similar procedures. Additionally, since STS cannot account for multiple valve procedures occurring concurrently, the surgical STS scores may be lower than the actual surgical risk involved in receiving multiple valve replacements.

Based on prior studies, patients diagnosed with left sided IE have more severe preoperative symptoms than those with right sided IE (Musci et al., 2007). Since the more severely infected patients with IE are operated on, we predicted that the surgical patients would also present with a complicated post-operative course (Byrne et al., 2011). Our data showed that surgical patients did experience significantly higher rates of MI, ESRD, and recurrence of infection at both 30 days and 1 year post-operatively. However, our data shows that medical patients had a significantly higher mortality rate at both 30 days and 1 years post-operatively.

This is an interesting finding because even though the surgical patients have significantly higher rates of post-operative complications, those complications can be managed without mortality, which provides evidence that surgical valve replacement may be superior to medical management. The medical patients succumb to their IE and experience mortality at a much higher rate, showing that IE is very severe and shows a rapid clinical course.

Most of the secondary outcomes of the study were experienced within 30 days in both the cohorts. For example, thirty (30) surgical patients exhibited septic shock in the first 30 days but only four (4) experienced septic shock between 30 days and 1 year. This trend is seen again in the surgical population when twenty nine (29) patients experienced an MI in the first 30 days and only three (3) experienced an MI between 30 days and 1 year. In the medical cohort, a similar pattern emerges where in the first 30 days fourteen (14) patients experience septic shock and only three (3) experience septic shock between 30 days and 1 year. This keys in on the importance of the first 30 days post-treatment. If patients are closely monitored post-operatively and post medical therapy, there is a very high likelihood that they will not experience adverse clinical outcomes within the next 11 months. An important distinction to be made is that this trend is not true for all post-treatment outcomes. The occurrence of stroke in surgical patients is very high between 30 days and 1 year. At 30 days, only ten (10) surgical patients presented with stroke but between 30 days and 1 year, twenty (20) new patients presented with stroke, which is clinically concerning. Surgical IE patients will need to be closely monitored for the presentation of stroke post-operatively and be treated accordingly. Clinicians are aware of these developments and preventative measures have also been considered (Thuny, 2005).

The Cox Regression Analysis conducted at 1 year post-operatively for the surgical cohort showed that age and pre-operative ESRD contribute to an increase risk of mortality. This was expected as increasing age adds significant risk to the long term outcomes of surgical patients due to the increased operative risk. ESRD has also been shown to lead to deleterious outcomes in patients contracting IE and needing valve

replacement surgery (Rekik et al., 2009). Additionally, our analysis returned showing that patients with hypertension had a decreased risk of mortality post-operatively. This was unexpected as preoperative hypertension is a severe medical condition and is worth examining further to determine if in fact there is a significant effect of IE patients.

Our Cox Regression Analysis for medical patients at 30 days showed that patients with a valvular abscess are at a significant risk of mortality. Our data and prior research suggests that the presence of a valvular abscess in IE cases is severe and should urgently be treated (Knosalla, 2000). This increase in risk that was found in our data paired with the high mortality rate for patients in the medical cohort, suggests that patients presenting with valvular abscess should be treated surgically for a valve replacement. Of the eight (8) medical patients presenting with a valvular abscess, five (5) passed away within 30 days and six (6) passed away within 1 year. Following valve replacement surgery only three (3) of the sixty six (66) surgical patients passed away within 30 days and ten (10) passed away within 1 year, which is a significant difference. This grim prognosis of medically treated patients suggests that any future patient presenting with left sided valvular abscess for IE be treated surgically instead of with antibiotics.

The high risk of operative mortality is often considered as the main reason to not operate on a patient. Many IE patients are consulted for surgery and the decision is ultimately made to not operate and treat medically based on this risk. In our surgical cohort, we had fifty four (54) surgical patients who presented with an STS score above 8, deeming them high risk. Out of those fifty four (54) patients, six (6) died (11.11%) within the first 30 days and (sixteen) 16 died (29.63%) within 1 year. In our medical cohort, we

had forty two (42) patients presenting with a high risk STS score. Fourteen (14) died (33.33%) within 30 days and twenty two (22) died (52.38%) within 1 year. This data will aid clinicians and surgeons in the future in determining if they should operate on traditionally high risk patients. The difference in mortality between the high risk surgical and medical patients is significant and offers concrete data as to why it may benefit patients with left-sided IE to undergo valve replacement surgery.

MRSA patients presented with the highest STS scores for both the surgical and medical cohorts. Despite this high operative risk, at 30 days it presented with the lowest rate of surgical mortality (4.76% for MRSA compared to 5.97% for Streptococcus and 9.26% for Staphylococcus). The 30 day medical mortality rate was 45.71% for MRSA, 11.36% for Streptococcus, and 34.15% for Staphylococcus, which are all higher than the pathogen specific surgical mortality rate at 30 days. Although all pathogen specific mortality rates are higher, the MRSA and Staphylococcus differences were statistically significant. This distinction endorses MRSA and Staphylococcus IE as being more severe compared to Streptococcal infection. Prior studies have suggested this notion and our study provides further evidence to support that claim (Han et al., 2017).

The 1 year mortality data in each of these cohorts follows a similar trend and is significant across all 3 pathogens. 28.57% of surgical MRSA patients died compared to 74.29% of medical MRSA patients, 7.46% of surgical Streptococcal patients died compared to 20.45% of medical Streptococcal patients, and 21.30% of surgical Staphylococcal patients died compared to 51.22% of Staphylococcal medical patients. The higher rates of mortality between the three most commonly occurring pathogens

found in IE can be used as a potential reference for future cases of IE with other pathogens. Based on our data, more studies on different pathogens can be conducted to determine if this trend is consistent.

As mentioned earlier, negative post-treatment surgical outcomes were significantly higher than the negative post-treatment medical outcomes. The most noteworthy trend this data showed is the recurrence of infection in surgical patients. All pathogen specific surgical patients exhibited significantly higher rates of recurrence of infection at 30 days and 1 year. This demonstrates that although surgery is effective in preventing mortality at 30 days and 1 year, there is concern for reinfection and potential recurrence of IE. Despite these high numbers of recurrence clinicians are able to still keep mortality rates significantly lower for surgical patients, which further suggests that once the initial pervasive infection is treated, any secondary infection can be slowed. Seven (7) surgical MRSA patients experienced recurrence of infection at 30 days and only two (2) experienced between 30 days and 1 year. In the Streptococcal population, eight (8) patients presented with infection within 30 days post-operatively and two (2) presented with infection between 30 days and 1 year. This keys in on the importance of immediate post-operative monitoring of infection and the certainty that all of the vegetation was removed during the operation. In the medical cohort, zero (0) MRSA patients presented with recurrence of infection at 30 days and 1 year and only two (2) Streptococcal patients presented with infection recurrence within 1 year. This suggests that long term antibiotic therapy is effective at clearing the infection, but may not act quick enough to prevent other complications such as stroke, embolic events, or septic

shock from causing mortality. This is an important distinction that this study wishes to emphasize. Surgical intervention is more efficacious in preventing mortality in left sided IE patients. Medical therapy is effective in clearing the infection over the course of the regimen. Patients in the medical cohort were prescribed various combinations of vancomycin, gentamicin, penicillin, oxacillin, ceftriaxone, and rifampin for an average of 5 weeks. Thirty five (35) patients (29.17%) in the medical cohort perished within 30 days and before the full course of antibiotics could be completed. As mentioned in the methods section, the 30 day window was started once there was a positive blood culture and a definitive vegetation confirmed by TEE or TTE. Based off of our results, these patients may have benefitted by surgical intervention and valve replacement instead of medical therapy.

Our study is not without major limitations. Since this was a retrospective analysis, we were limited in how much data we could collect from chart review. Many patients from the initial 1210 had to be excluded due to lack of follow up, inconclusive diagnosis of definite IE, and lack of preoperative characteristics and baseline data. This study could be much stronger if our sample size was larger and included patients with more robust data. Our decision to include only patients diagnosed with MRSA IE, Streptococcal IE, and Staphylococcal IE may be viewed as a limitation, but we believe that it is more pertinent to address the most common pathogens and how they are treated medically and surgically rather than include a wide range of pathogens with different responses to medical therapy. The definition and categorization of patients in the medical cohort can be viewed as another limitation. It was difficult to decide on how the 30 day and 1 year

window would be defined for the medical patients. Many patients were started on antibiotic therapy when they presented with bacteremia prophylactically before there was a positive TTE or TEE confirming valvular IE. We decided to make the start date or operative date on these patients as the first day that they presented with a positive TTE or TEE for valvular IE as that would be the first day that valve replacement would be considered as an option. We understand the difficulty in assessing the efficacy of medical management based on this decision, but remained consistent throughout our analysis and present the data with full transparency as to our rationale and logic surrounding this determination. Additionally, our institution is a high volume referral hospital where very severely ill patients are referred for treatment. The severity of IE in this population may be higher than the severity in other institutions and should be factored in to the interpretation of data. Even with this increase in severity, the surgical patients still outperformed the medical patients in survival at 30 days and 1 year after addressing the surgical risk and preoperative severity of infection. To our understanding, this study offers a comprehensive view of surgically and medically treated IE patients with a full evaluation of post-treatment outcomes.

This significant difference in mortality, coupled with the performance of high risk surgical patients and the fact that the surgical patients all had higher rates of preoperative fever, angina, and valvular abscess, provides strong evidence to the benefit of surgical intervention compared to medical management for treatment of left sided IE. The first 30 days post-treatment for IE, as highlighted above, is key in maintaining and controlling the disease. Surgical intervention, even with its drawbacks with post-operative complications

of septic shock, stroke, and MI, offers an immediate eradication of the disease and a method of decreasing the mortality rate in the population. Future studies should be conducted on this topic to confirm our observations and determine if a trend in the data can be corroborated.

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