APPROPRIATENESS OF PREOPERATIVE ANTIMICROBIAL THERAPY DOES NOT IMPACT OUTCOMES FOLLOWING SURGERY FOR INFECTIVE ENDOCARDITIS

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by

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ABSTRACT

APPROPRIATENESS OF PREOPERATIVE ANTIMICROBIAL THERAPY DOES NOT IMPACT OUTCOMES FOLLOWING SURGERY FOR INFECTIVE ENDOCARDITIS

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The University of Texas Southwestern Medical Center, 2017

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Background: A long-standing paradigm of the surgical management of infective endocarditis was to delay surgery until the infection was adequately treated out of concern for increased technical difficulties due to acutely inflamed valvular tissue present during active infection. Up to half of patients with infective endocarditis may initially receive bacteriologically inadequate antimicrobial therapy, delaying time to surgery in these patients. However, several benefits of earlier surgery in certain patients with infective endocarditis and guideline-directed indication(s) for surgery have emerged over the last decade. Thus, surgeons are increasingly faced with a decision whether to operate on patients with infective endocarditis whose infection may not be adequately treated prior to surgery.

Objective: We sought to examine the characteristics of patients with infective endocarditis requiring surgical treatment and to determine whether the appropriateness of preoperative antimicrobial therapy impacted their short-term and long-term outcomes.

Methods: Records of 335 consecutive patients undergoing valve surgery to treat infective endocarditis between 1990-2013 at a single center were retrospectively reviewed. All patients with definite or possible infective endocarditis, defined by modified Duke criteria, and with positive blood cultures prior to surgery were included in the study. Two infectious disease clinicians, blinded to patient outcomes, graded appropriateness of preoperative antimicrobial regimens.

Results: A total of 270 patients (190 men; mean age 46.2 years) met inclusion criteria. Appropriate preoperative antimicrobial therapy was administered to 217 (80%) patients. Enterococci and fungal infections were more common in the inappropriately treated group, as was recurrent infective endocarditis. A history of viral hepatitis was less common in the inappropriately treated group. Otherwise, there were no significant differences in the rates of baseline comorbidities, valve involvement, or etiologic microorganisms among the groups. Operative mortality was 12.9% overall, with no significant difference between the appropriately (14%) and inappropriately (8%) treated groups (p=0.28). There was no difference in unadjusted, all-cause, five-year survival between the appropriately (48%) and inappropriately (52%) treated groups (log-rank p=0.30).

Conclusion: There were no significant differences in short- and long-term mortality between patients receiving appropriate versus inappropriate preoperative antimicrobial therapy prior to valve surgery for infective endocarditis. Surgeons should not hesitate to operate on patients with infective endocarditis and a guideline-directed indication for valve surgery, even if their preoperative antimicrobial regimen has been inadequate.

TABLE OF CONTENTS

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CHAPTER 1: INTRODUCTION

Infective endocarditis (IE) is a high-risk pathology associated with a severe in-hospital mortality rate that has remained between 10-20% for more than twenty years despite the continued evolution of both medical and surgical approaches to this disease.[1,2,3] Recent large scale studies have identified an increased incidence of IE over the last several decades, now as high as 3-10 per 100,000 in the general population per year.[4,5,6] Not only has the incidence of IE been increasing over time, but the disease has simultaneously shifted to an entirely different presentation than that which was classically described. Whereas IE traditionally affected young adults with underlying rheumatic heart disease or congenital heart disease, IE now primarily affects older patients with a higher burden of comorbidities and an entirely different set of risk factors, including prosthetic heart valves, immunosuppressive therapy, and history of intravenous drug abuse.[7] Interestingly, staphylococci have also surpassed oral streptococci as the most common etiologic microorganism in diagnosed cases of IE.[1]

Due to the complexity and relative rarity of the disease, the diagnosis and management of patients afflicted by IE remains a significant challenge. Unfortunately, the majority of patients with IE are initially managed by a variety of providers with limited expertise related to diagnosing and treating IE, which potentially delays definitive diagnosis and increases the likelihood that guidelines related to antibiotic therapy and surgical indications are not properly followed.[8] Inspired by the "heart valve team" concept developed during the rise of transcatheter aortic valve replacement, recent proposals for the formation of "IE teams" at hospitals facing a heavy burden of IE patients have been put forth to address this issue.[9] These multidisciplinary teams can include general and imaging cardiologists, cardiothoracic

surgeons, infectious disease specialists, microbiologists, nephrologists, neurologists, and radiologists so that a comprehensive assessment of the patient can be rapidly completed and an effective, efficient plan of care can be delivered quickly.[3]

Indeed, the evidence supports the effectiveness of the multidisciplinary IE team in reducing both in-hospital and longer-term mortality related to IE. Chirillo *et al.* were able to reduce in-hospital (28% vs. 13%; p=0.02) and 3-year (34% vs. 16%; p<0.001) mortality after the formation of an IE team that met weekly to review hospitalized patients, provided initial evaluation within 12 hours of suspicion for IE, and performed early interventions for those patients with surgical indications.[8] Similarly, Botelho-Nevers *et al.* reported that a multidisciplinary IE team reduced in-hospital (12.7% vs. 4.4%; p=0.007) and 1-year (18.5% vs. 8.2%; p=0.008) mortality after standardizing care for patients admitted with IE, including medical management protocols and indications for surgery.[10]

Beyond the dramatic reduction in mortality observed in these studies, another key finding in the study by Botelho-Neveres *et al.* is of particular interest. This group documented that prior to the formation of their IE team and standardization of their antimicrobial protocols, appropriate antimicrobial therapy was prescribed to patients in only 32% of cases.[10] Despite this initially poor compliance with published guidelines, the correct antimicrobials were prescribed with 95% compliance after implementation of the IE team. Although it may be surprising that inappropriate antimicrobial agents were prescribed so often in the first phase of the study, this finding is consistent with several other reports that have investigated how often patients with severe infections are prescribed inappropriate antibiotics. These studies have demonstrated that up to half of patients admitted to the intensive care unit with severe

infections receive inappropriate antimicrobial therapy.[11,12] Not surprisingly, these reports have also concluded receiving appropriate antimicrobial therapy is associated with improved outcomes.

Because antimicrobial therapy with prolonged administration of bactericidal agents remains the foundation of therapy for all IE patients,[13] it is reasonable to expect that appropriately targeted antimicrobials would also reduce mortality related to IE. Indeed, it was recently demonstrated by Fayad *et al.* that appropriate antimicrobial therapy, defined as bacteriologically effective therapy in both the preoperative and postoperative periods and postoperative therapy of sufficient duration according to international guidelines, significantly improved the prognosis of patients with IE undergoing valve surgery.[14] These authors found that appropriate antimicrobial therapy was administered to patients at a rate of 71% at their center and that patients receiving appropriate antimicrobials were at lower risk for operative mortality after controlling for potentially confounding factors (adjusted odds ratio 0.35, 95% confidence interval 0.14-0.84; p=0.02).

The work of Fayad *et al.* is also noteworthy because the authors focused on the outcomes of patients with IE who ultimately required surgical treatment for their disease. Surgery is reserved for patients with specific indications such as progressive valve and/or tissue damage, uncontrolled infection, and high risk for embolism. The goals of surgical treatment of IE include the removal of all infected tissue and prosthetic material, debridement of paravalvular infections and cavities, restoration of cardiac valve function, and removal of potential sources of emboli.[3] In recent years, surgery has emerged as a valid therapeutic modality for an increasing number of indications, and more than 50% of IE patients now undergo surgery.[15,16]

Although surgical management of IE has increased over the last several decades, outcomes of valve surgery for indications related to IE remain inferior as compared to elective valve surgery for other indications. Survival following surgery for IE is usually reported >80% at 6 months, but 10-year survival in the majority of studies with long-term outcomes data is between 40-60%.[17,18]

Despite the potential of surgical therapy to secure improved outcomes for patients with IE, few high quality randomized trials are available to clarify important risk factors, proper indications, or optimal timing for surgical therapy. Nevertheless, the limited evidence available, which is primarily derived from historical observational studies of single-center experiences, suggests certain patients do benefit from surgical intervention. Some have suggested that the limitations inherent in the currently available level of evidence to support surgical therapy for IE may reduce compliance with the current guidelines.[19] Indeed, an international, multicenter assessment of the "real-world" compliance with surgical guidelines identified that 24% of IE patients with an indication for surgical intervention did not undergo surgery.[16]

Another potential explanation for the limited compliance with surgical indications for IE is the practice momentum of the traditional surgical dogma to avoid operating during active IE infections in favor of so-called "late" surgery for patients who survive the acute phase of infection but sustain lasting damage to cardiac valve structures. [20,21] "Early" surgery during active infection has been traditionally felt to be too risky due to the acute inflammatory status of the patient's valve tissue that significantly increased the technical difficulty of the operation and, in turn, increased the risk of postoperative morbidity and mortality.

Despite this long-held surgical approach to IE, significant evidence to support the use of early surgery has begun accumulating in recent years. A landmark randomized control trial performed in South Korea compared early surgery (surgery performed within 48 hours for patients with severe valve disease and large vegetations) versus conventional medical treatment in cohorts of 37 and 39 patients, respectively.[20] The authors of this study reported that the patients assigned to early surgery were at significantly lower risk for the combined endpoint of in-hospital death and embolic events within 6 weeks of randomization (hazard ratio 0.10; 95% confidence interval 0.01-0.82; p=0.03) as well as the combined endpoint of all-cause mortality, embolic events, and recurrence of IE at 6 months (hazard ratio 0.08; 95% confidence interval 0.01-0.65; p=0.02). Moreover, 77% of the patients initially randomized to the conventional treatment control arm eventually required surgery during the study follow-up period, usually during their index hospitalization. Because the patients enrolled in this study were relatively young (mean age 46 years) and healthy (low incidences of diabetes, hypertension, and coronary artery disease as compared to international epidemiological studies of IE), the ability to generalize these results to all IE patients with surgical indications is limited. Nevertheless, this study and other retrospective analyses[22] have supported an expanded role for early surgery in patients with IE.

Several risk scores have also been developed to assist clinicians when making the difficult decision about whether to treat IE with surgery. However, a tradeoff exists among the published risk scores between specificity of risk factors included in the models and the generalizability of the models themselves because scores developed from larger populations tend to lack key specific details regarding patient characteristics. Gaca *et al.* have developed

the most robust risk score, using the Society of Thoracic Surgeons Adult Cardiac Surgery Database to identify over 19,000 operations for IE.[23] However, this score lacks adjustment for important characteristics such as etiologic microorganisms and valve type (native versus prosthetic valve IE). This significantly limits the practicality of the Gaca risk score because, for example, both prosthetic valve endocarditis[24] and Staphylococcus aureus endocarditis[25] are associated with increased morality as compared to native valve endocarditis and Streptococcal endocarditis, respectively.

Other risk scores that do account for etiology and valve type have been developed from smaller populations, limited to only 400 patients in each study, but these efforts lack external validation to prove their generalizability outside of the original study population.[26,27] Furthermore, these risk scores are focused only on short-term, in-hospital outcomes rather than long-term survival, and none were developed while accounting for the appropriateness of antimicrobial therapy prescribed to patients undergoing surgery, a potential confounding factor that can reasonably be expected to affect outcomes.

Thus, cardiothoracic surgeons consulted regarding patients with IE are now commonly faced with several dilemmas. First, it is difficult to predict the patient's prognosis should they undergo surgery, given the significant limitations of the currently available risk models. Second, the optimal timing of surgery requires a balance between a variety of important factors. Delaying surgery may provide several advantages including the delivery of antimicrobial therapy for longer duration to treat the infection and reduce associated inflammation and the chance to achieve hemodynamic stabilization in critically-ill patients. On the other hand, early surgery reduces the progression of IE and associated valvular

destruction, abscess formation, heart block, and embolic complications.[3]

This decision becomes even more complicated if the surgeon discovers that the referred patient has been prescribed inappropriate antimicrobial agents, which, as described above, occurs quite frequently. Should the surgeon delay surgery for such patients to allow for proper targeting of the etiologic microorganism with antimicrobial therapy for some duration prior to the intervention? As discussed above, Fayad *et al.* have demonstrated that patients receiving appropriate antibiotics (in both the preoperative and postoperative period) have better outcomes following valve surgery for IE than those who receive inappropriate antibiotics.[14] But, the decision to perform valve surgery must, by definition, be made without knowledge of the appropriateness of postoperative antimicrobial therapy. Therefore, the goal of this study was to assess the impact of the appropriateness of isolated preoperative antimicrobial therapy on outcomes of patients undergoing surgery for IE at a single-center over several decades. In addition to short-term outcomes, which are commonly assessed when IE is studied, we also sought to describe the long-term postoperative outcomes of these patients.

CHAPTER 2: METHODS

Study Design and Population

This investigation was approved by the local Institutional Review Board at the University of Texas Southwestern Medical Center, and patient informed consent was waived due to the retrospective nature of the study. A retrospective review of a prospectively maintained database of patients undergoing surgery for IE was performed. Between 1990 and 2013, 335 consecutive patients underwent valve surgery for IE at a single quaternary referral center. Patients were identified as having IE if they met the modified Duke criteria for definite or possible endocarditis (Table 1).[28] Clinical information about each patient was recorded, including patient comorbidities, risk factors for IE, blood culture results, antimicrobial susceptibility testing, affected valves, preoperative antimicrobial therapy, and mortality.

Table 1. Duke Criteria for the Diagnosis of Infective Endocarditis (IE). [Adapted from 28]

Definite diagnosis of IE
Pathological Criteria (1) Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or (2) Pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis *Clinical Criteria* (2 major, 1 major and 3 minor, or 5 minor required) <u>Major Criteria</u> (1) Blood Culture Positive for IE, defined as follows: (a) Typical microorganisms consistent with IE from 2 separate blood cultures: Viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphlococcus aureus*; or community-aquired enterococci, in the absence of primary focus (b) Microorganisms consistent with IE from persistently positive blood cultures, defined as follows: At least 2 positive cultures of blood samples draw >12 hr apart; or

All 3 or a majority ≥4 separate cultures of blood (with first and last sample draw at least 1 hr apart)

(c) Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer >1:800

(2) Evidence of endocardial involvement

(3) Echocardiogram positive for IE, defined as follows:

(a) Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the abscen of an alternative anatomic explanation; or

(b) Abscess; or

(c) New partial dehiscence of prosthetic valve

(4) New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)

Minor Criteria

(1) Predisposition: predisposing heart condition or injection drug use

(2) Fever: temperature >38°C

(3) Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeways's lesions

(4) Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and reheumatoid factor

(5) Microbiological evidence: positive blood culture but does not meet major criterion as noted above or serological evidence of ative infection with organism consistent with IE

Possible diagnosis of IE

Clinical Criteria (see above; 1 major and 1 minor or 3 minor required)

Rejected diagnosis of IE

(1) Firm alternate diagnosis explaining evidence of IE; or

(2) Resolution of IE syndrome with antibiotic therapy ≤4 days; or

(3) No pathologic evidence of IE at surgery or autopsy, with antibiotic therapy ≤4 days; or

(4) Does not meet criteria for possible IE, as above

Surgical intervention and its timing were guided by international guidelines published by the Society of Thoracic Surgeons,[29] the European Society of Cardiology,[30] and especially the American Heart Association (Table 2).[31] The goal of surgical therapy was to perform radical debridement of infected tissue with reconstruction of cardiac valves via repair or

replacement, when necessary. Allografts, xenografts, bioprostheses, and mechanical prostheses were implemented according to surgeon preference. Valve repair was performed when small, isolated valvular lesions, infected tissue, and vegetations could be adequately removed to allow for repair.

Table 2. 2015 American Heart Association guidelines for surgical indications to treat infectious endocarditis [adapted from 31].

Surgical Indication		Class*, Level of Evidence†
Heart Failure	Valve dysfunction resulting in symptoms or signs of heart failure	I, B
	Prosthetic valve endocarditis with symptoms or signs of heart failure resulting from valve dehiscence, intracardiac fistula, or severe prosthetic valve dysfunction	I, B
Uncontrolled Infection	Complications of heart block, annular or aortic abscess, or destructive penetrating lesions	I, B
	Relapsing prosthetic valve endocarditis	IIa, C
	Endocarditis due to fungal infection or infection with highly resistant organisms	I, B
	Persistent infection (manifested by persistent bacteremia or fever lasting >5 days, provided that other sites of infection and fever have been excluded) after the start of appropriate antibiotic therapy	I, B
Prevention of Embolism	Recurrent emboli and persistent or enlarging vegetations despite appropriate antibiotic therapy	IIa, B
	Severe valve regurgitation and mobile vegetations >10 mm	IIa, B
	Mobile vegetations >10 mm, particularly when involving the anterior leaflet of the mitral valve and associated with other relative indications for surgery	IIb, C

*Class I guidelines indicate surgery should be performed. Class IIa guidelines indicate it is reasonable to perform surgery. Class IIb guidelines indicate it is not unreasonable to perform surgery.

†No Level of Evidence A recommendations are present. Level of Evidence B indicates supportive data is derived from a single randomized study or multiple nonrandomized studies. Level of Evidence C indicates supportive data is derived from consensus opinions of experts, case studies, or historical standard of care.

Microbiology and Antimicrobial Assessment

All blood cultures were routinely processed in clinical microbiology laboratories and incubated in an automated monitoring system for a minimum of five days. The etiologic organism(s) and their antimicrobial susceptibilities were recorded. Some patients (n=65; 19%) never had positive blood cultures and were therefore reported as "culture negative." The majority of culture negative patients had inappropriately received antibiotic therapy before blood cultures had been drawn. Culture negative patients were not included in the final study cohort given the inherent difficulty in determining the appropriateness of antimicrobial therapy prescribed to these patients.

Antimicrobial regimens assigned to each patient were collected, including any agents for which a full course was completed preoperatively and any agents still being administered at the time of operation. Two infectious disease clinicians interpreted the appropriateness of each antimicrobial regimen. These clinicians were not part of the clinical care team for these patients and were blinded to clinical characteristics and outcomes for each patient (with the exception of etiologic organisms, their susceptibilities, valve status [native vs. prosthetic], and drug allergies). Each regimen was graded as appropriate antimicrobial therapy (AAT) or inappropriate antimicrobial therapy (iAAT) by the infectious disease specialists. Preoperative antimicrobial therapy was considered AAT if it was "bacteriologically effective" as defined by a prior study,[14] specifically: a regimen including antibiotic(s) proposed by international guidelines with evidence that the causative organism was in vitro susceptible to at least one of the antibiotics in the regimen.

Outcome Measures and Statistical Analyses

The primary end points were operative mortality, as defined by the Society of Thoracic Surgeons (i.e., all-cause mortality at 30-days or during the index hospital admission, whichever is longer), and all-cause long-term mortality. Survival was calculated as the number of days from the date of operation to the date of death from any cause. For patients whose medical record lacked documentation of survival on or death before 5-year follow-up, the Social Security Death Index was used to determine mortality. Surviving patients were censored at the date of last positive medical contact in the electronic medical record.

Baseline characteristics were described using means and standard deviations for continuous variables and proportions for categorical variables. Student's t-test was implemented to compare normally-distributed continuous variables, and χ^2 test was used to compare categorical variables. The primary comparison was between the AAT and iAAT cohorts. Kaplan-Meier analysis was performed to calculate cumulative survival and plot survival curves for the AAT and iAAT groups of IE patients. The log-rank test was used to compare differences between these curves. All comparisons were unpaired, and all tests of significance were two-tailed, with $p < 0.05$ considered significant. The statistical analysis software R 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria) was used to perform all analyses.

CHAPTER 3: RESULTS

Of the 335 patients with definite or probable IE by Duke modified criteria undergoing valve surgery during the study period, 270 (81%) had positive blood cultures that allowed for assessment of the adequacy of preoperative antimicrobial therapy. The mean age of these patients was 46.2 ± 14.3 years, and 190 (70%) were male. AAT was administered to 217 (80%) patients, and 53 (20%) patients were classified as iAAT. Indications for surgery included persistent infection despite antibiotic therapy, large vegetation size, congestive heart failure, recurrent embolization, annular abscess, and conduction abnormalities.

Baseline characteristics of the AAT and iAAT groups are presented in Table 3. Recurrent IE was more common in the iAAT group (AAT 18% vs. iAAT 34%; p = 0.01). The AAT group more commonly had a diagnosis of viral hepatitis B and/or C (AAT 27% vs. iAAT 11%; p = 0.03). There was also a trend towards increased history of intravenous drug in the AAT group, though it did not reach statistical significance (AAT 35% vs. iAAT 21%; p = 0.07). Otherwise, there were no significant differences in patient risk factors for IE or comorbidities prior to surgery.

Table 3. Baseline characteristics of AAT and iAAT groups.

Characteristic	**AAT** (N = 217)	**iAAT** (N = 53)	**p-value**
Male	152 (70)	38 (72)	0.94
Age (years)	45 ± 14	48 ± 15	0.92
IV Drug User	75 (35)	11 (21)	0.07
Hemodialysis	37 (17)	6 (11)	0.42
Hepatitis B or C	58 (27)	6 (11)	0.03
Diabetes Mellitus	47 (22)	11 (21)	1.00
CHF	156 (72)	42 (79)	0.39
RHD	7 (3)	4 (8)	0.30
Recurrent IE	38 (18)	18 (34)	0.01

Data presented as N (%) or mean ± standard deviation.

CHF congestive heart failure; RHD rheumatic heart disease

The anatomical and microbiological details of IE in our study population are presented in Tables 4 and 5, respectively. Native valves were involved in 219 (81%) patients. The mitral valve was the most commonly involved (159 patients; 59%), followed by the aortic valve (126 patients; 47%). Multiple valves were involved in 72 (27%) patients. There were no significant differences in the rates of specific valve involvement between the study groups.

Table 4. Anatomy of infective endocarditis in the AAT and iAAT groups.

Affected Valve	**AAT** (N = 217)	**iAAT** (N = 53)	**p-value**
Prosthetic valve	37 (17)	12 (23)	0.45
Affected valve			
Aortic	95 (44)	31 (58)	0.08
Mitral	130 (60)	29 (55)	0.57
Tricuspid	42 (19)	8 (15)	0.59
Pulmonary	10 (5)	1 (2)	0.61
Multiple valves	58 (27)	14 (26)	1.00

Data presented as N (%).

Staphylococcus aureus was the most common etiologic microorganism (104 patients; 39%), followed by Streptococci (73 patients; 27%), coagulase-negative Staphylococci (46 patients; 17%), and Enterococci (35 patients; 13%) organisms. A non-statistically significant trend towards Streptococci infections in the AAT group was apparent (AAT 29% vs. iAAT 17%; p = 0.07). Fungal (AAT 2% vs. iAAT 9%; p = 0.04) and Enterococci (AAT 10% vs. iAAT 25%; p = 0.01) infections were more commonly isolated in the iAAT group.

Table 5. Microbiology of infective endocarditis in the AAT and iAAT groups.

Etiologic Organism	**AAT** (N = 217)	**iAAT** (N = 53)	**p-value**
Staphylococcus aureus	87 (40)	17 (32)	0.36
MRSA	18 (8)	3 (6)	0.72
Coagulase-negative *Staphylococci*	38 (18)	8 (15)	0.67
Streptococcous spp	64 (29)	9 (17)	0.07
Enterococcus spp	22 (10)	13 (25)	0.01
Gram positive organisms	7 (3)	2 (4)	1.00
Cardiobacterium hominis[a]	2 (1)	0 (0)	1.00
Other Gram negative organisms	4 (2)	3 (6)	0.28
Fungi	5 (2)	5 (9)	0.04
Polymicrobial	13 (6)	7 (13)	0.13

Data presented as N (%).
MRSA methicillin-resistant *Staphylococcus aureus*
[a]part of HACEK group

In the study population, overall operative mortality was 12.9%, and 5-year mortality was 50.6%. There was no statistically significant difference in operative mortality between groups (AAT 14% vs. iAAT 8%; p = 0.28; Figure 1). There were no differences in long-term survival up to 10 years between the groups (log-rank p = 0.30; Figure 2). Mean follow-up time was 3.9 years (range from 0 days [operative mortality] to 20 years).

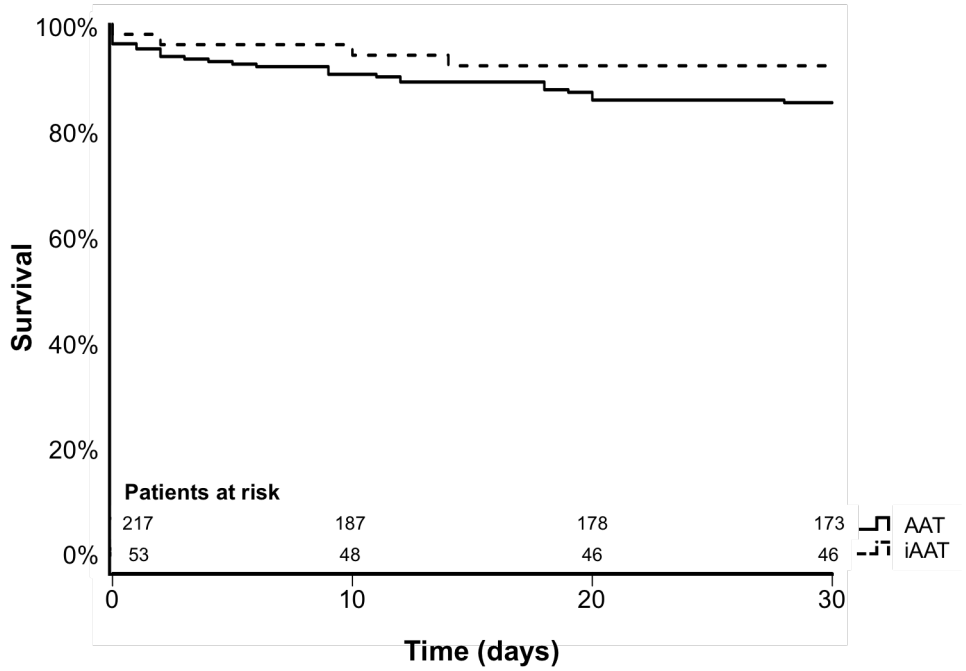

Figure 1. Kaplan-Meier estimates of survival for the appropriately (AAT; solid line) and inappropriately (iAAT; dashed line) treated groups in the 30 days following index valve surgery for infective endocarditis. There was no significant difference in operative mortality between the two groups.

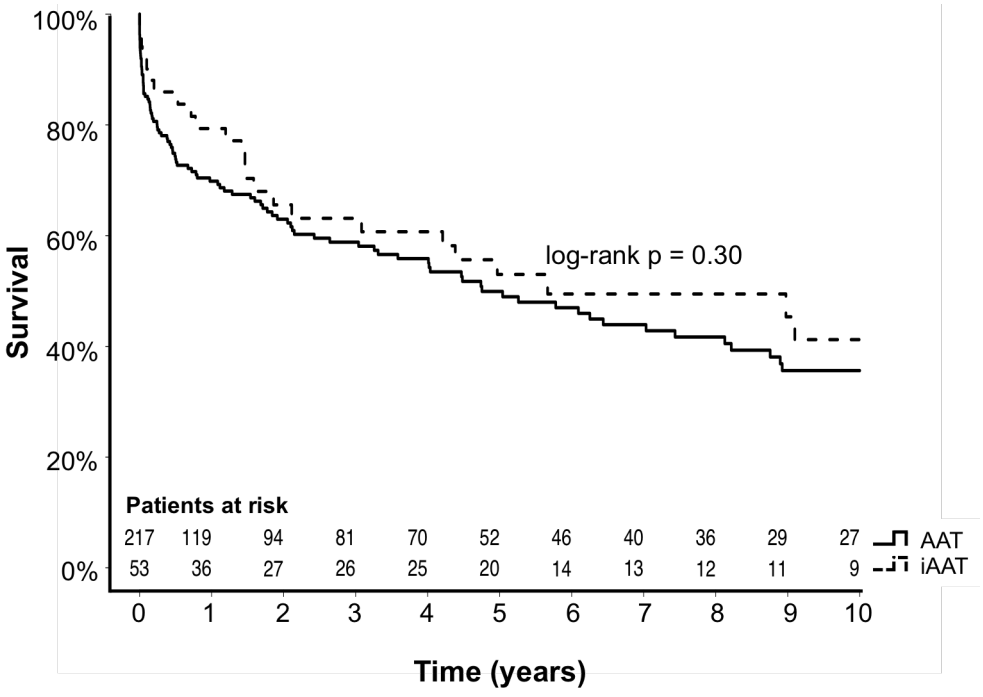

Figure 2. Kaplan-Meier estimates of survival for the appropriately (AAT; solid line) and inappropriately (iAAT; dashed line) treated groups up to 10 years following index valve surgery for infective endocarditis. There were no significant differences in long-term survival between the two groups.

Given that the study duration extended over 24 years during which both the clinical presentation and standard of care for IE patients changed, several trends over the study period were also investigated (Figure 3). The percentage of patients receiving AAT varied from a nadir of 71% from 2000 to 2004 (in the middle of the study period) to a maximum of 89% from 2010 to 2013, though no clear trend in percentage of patients receiving AAT emerged over the study period. On the other hand, a trend was evident in the incidence of operative mortality, which decreased from 16.7% in the first five years of the study period to 2.8% from 2010 to 2013.

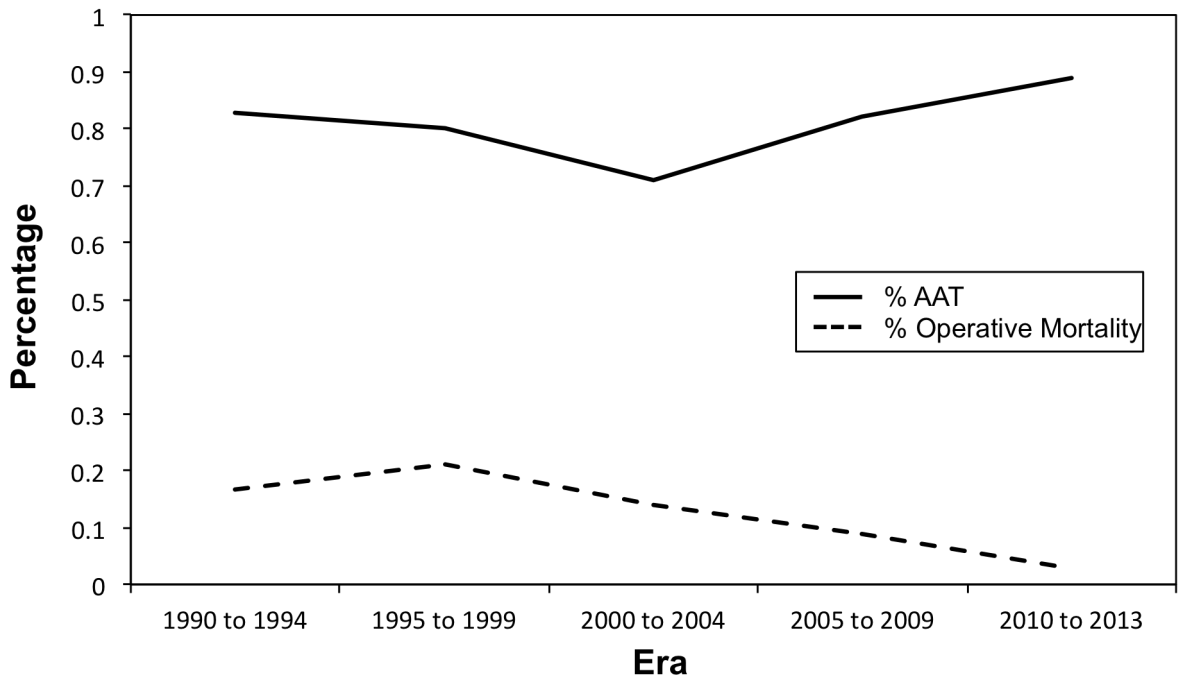

Figure 3. Trends in the number of patients who received appropriate antimicrobial therapy (AAT) and patients who suffered operative mortality over the duration of the study period. The 23-year study period was separated into periods of 5 years.

CHAPTER 4: CONCLUSIONS & RECOMMENDATIONS

IE is a complex disease associated with a high mortality and severe complications.[1] Because a multidisciplinary approach is required to provide comprehensive, efficient care to patients with IE, an "IE team" model has recently been proposed and demonstrated to improve outcomes of patients with IE.[8,9,10] In particular, previous investigations have identified that IE team approaches can improve antimicrobial selection.[10] Given that surgeons are increasingly faced with a decision whether to perform surgery during the acute phase of IE despite decades of surgical dogma,[20,21,22] appropriate antimicrobial selection may be a key consideration in a patient under consideration for surgery because effective antimicrobials may provide some relief to the inflammatory milieu of the active infection. This consideration is especially important given that up to half may initially be prescribed inappropriate antibiotics.[10,11,12,14]

Therefore, we sought to describe our center's experience in the surgical management of IE over several decades and to determine whether antimicrobial selection prior to surgery affected short and long-term outcomes of patients undergoing valve surgery to treat IE. The cohort of patients with IE presented in this study is, to our knowledge, one of the largest series reported in the literature.[32,33] Although this study again highlights the high mortality rate associated with valve surgery for IE, our analysis determined that the appropriateness of preoperative antimicrobial therapy did not affect short nor long-term mortality.

There are many variables surgeons must weigh when considering surgical treatment of IE. Because of the dearth of randomized trials investigating optimal indications and timing for surgery,[20] it remains challenging to predict outcomes for individual patients undergoing valve

surgery for IE. Although a high-quality model was recently developed to assist surgeons in risk assessment for potential surgical candidates, this model was developed from a database that lacked potentially key information relevant to outcomes including etiologic microorganisms and valve status (native versus prosthetic).[23] Moreover, the model only predicts operative outcomes and cannot provide information regarding long-term survival. Other models are limited by the small sample sizes from which they were generated, limiting their generalizability to other populations and preventing independent validation.[26,27] None of the published models account for appropriateness of antimicrobial therapy. Therefore, surgeons must often rely on observational studies, expert opinion, and anecdotal experiences to identify potential risk factors for poor surgical outcomes in patients with IE.

Very limited evidence is available to assess how antimicrobial therapy affects surgical outcomes in IE. Reports documenting outcomes of patients with severe infections requiring admission to intensive care units have demonstrated that appropriate antimicrobial therapy significantly improves patient prognoses.[11,12] Therefore, it may be reasonable to conclude patients with IE receiving appropriate antimicrobial treatment would experience a benefit as opposed to those receiving inadequate therapy, even if the infection is treated surgically. Indeed, Fayad *et al.* have outlined results from a single European center suggesting that overall adequate antimicrobial therapy, defined as appropriate treatment in both the pre- and postoperative phases, significantly improves the short-term prognosis of patients undergoing valve surgery for IE (adjusted odds ratio 0.34, 95% confidence interval 0.14-0.84, p = 0.02).[14,34] At the time a decision about whether to offer surgery is required, however, clinicians can only assess the adequacy of preoperative antimicrobial therapy. Furthermore,

no studies have previously assessed how antimicrobial therapy affects long-term outcomes of surgery for IE. Therefore, we sought to investigate how isolated preoperative antimicrobial treatment affects both short and long-term outcomes following surgery for IE in our study.

Several similarities and differences between our study and the data published by in the previous report assessed the effect of antimicrobial therapy on operative outcomes[14] are notable. Overall operative mortality in our cohort (12.9%) is similar to that reported by Fayad *et al.* (15%). The proportion of isolated etiologic organisms (Streptococci [37%] was the most common etiologic microorganism in the Fayad study) and the number of intravenous drug users (2% in the Fayad cohort versus 32% in our cohort) varied significantly between the studies. These findings likely reflect the different profile of IE in North America as compared to Europe.[1] The overall antimicrobial therapy was considered adequate in 70.5% of the cases reported by Fayad et al., but the majority of inadequate regimens were deemed as such due to insufficient postoperative duration of therapy and not due to inappropriate selection of agent(s).[14] In our analysis, 80% of the preoperative antimicrobial regimens were adequate; thus 20% of the time an inappropriate selection was made regarding antimicrobial selection. Postoperative therapy was not assessed because, by definition, knowledge regarding postoperative medical therapy cannot exist at the time a surgeon must decide whether to offer surgery to a patient with IE. Finally, Fayad et al. did not report specific characteristics of the AAT and iAAT groups, an important limitation to the study as the differences in outcomes identified among these groups could potentially be explained by a variable other than appropriateness of antimicrobial therapy.

In our cohort, the iAAT group disproportionately included patients with recurrent IE as

well as patients with Enterococci and fungal IE. The group receiving AAT disproportionately included patients with a history viral hepatitis, with trends towards increased prevalence of intravenous drug use and IE due to Streptococci. On the other hand, there were no differences in proportion of affected valves or prosthetic valves between the groups. How these differences in cohort characteristics affected outcomes could not be determined by our analysis due to the limited number of events over the study duration. Nevertheless, these findings suggest that clinicians treating patients with recurrent, Enterococci, or fungal IE should pay particular attention to ensure that appropriate antimicrobial therapy has been prescribed to their patients, regardless of a patient's candidacy for surgery.

Historically, the dogma of surgeons was to decline surgery during active IE episodes out of concern for severe tissue infection and inflammation that would increase the technical difficulty of the operation and result in increased postoperative mortality.[20,21] More recently, however, early surgical therapy during the active IE infection is increasingly being performed[1,15] given surmounting evidence of its benefit in select patients.[20,21] Our study did not investigate the timing of surgery, but the results of the study may indirectly support the evident trend towards early surgery. Presumably, patients receiving iAAT prior to surgery may have persistent infection causing increased inflammation as compared to those with AAT. Short and long-term mortality were no different between these two groups in our cohort, however, suggesting that modern surgical techniques are capable of overcoming the severe inflammation associated with active IE. Moreover, although no clear trend towards improvement in preoperative antimicrobial therapy was evident, trend towards decreasing operative mortality was evident in our cohort, suggesting the historical surgical dogma may

no longer apply to patients with IE.

Limitations of this study include those expected of a single-center, retrospective study. The generalizability of these results to other centers cannot be ensured. Moreover, the study period captures nearly two and half decades of changes in medical and surgical management of IE as well as changes in the clinical presentation of IE. Therefore, the therapy offered to patients earlier in the study may not match the standard of care practiced today. As no assessment of antimicrobial dosing or duration was performed, our definition of appropriate antimicrobial therapy may appear insufficiently precise in comparison to current guidelines. However, our definition matches the one used in most studies on the adequacy of antimicrobial therapy.[14,34,35,36] Given the long duration of the study period, specific information regarding whether patients had cleared their bacteremia and the timing of clearance in relation to surgery was often not available and could not be included in the analysis. Finally, it is important to highlight that, despite the findings reported, it remains essential to offer all patients with IE appropriate antimicrobial therapy according to international guidelines[29,30,31] and local institutional policy.

In conclusion, short and long-term outcomes of patients undergoing valve surgery to treat IE are not affected by the appropriateness of their preoperative antimicrobial regimen. Therefore, our results suggest that surgeons should not hesitate to operate on a patient who has an guideline-directed indication for surgery, even if that patient has not been treated with appropriate antimicrobial therapy for a sufficient duration prior to the operation.

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGMENT

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VITAE

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