**AUS DEM LEHRSTUHL
FÜR INNERE MEDIZIN I
DIREKTOR: PROF. DR. MED. JÜRGEN SCHÖLMERICH
DER MEDIZINISCHEN FAKULTÄT
DER UNIVERSITÄT REGENSBURG**

10-Year Epidemiology of Infective Endocarditis – Correlations between Histopathology, Microbiology and Clinical Presentation

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10-Jahres Epidemiologie der Infektiösen Endokarditis – Vergleich zwischen Histopathologie, Mikrobiologie und klinischer Präsentation

**Inaugural-Dissertation
zur Erlangung des Doktorgrades
der Medizin**

**der
Medizinischen Fakultät
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**vorgelegt von
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Dekan:	**Prof. Dr. med. Bernhard Weber**
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2. Berichterstatter:	**Prof. Dr. med. Christof Schmid**
Tag der mündlichen Prüfung:	**15. 01. 2010**

Es ist nicht genug, zu wissen, man muß auch anwenden; es ist nicht genug, zu wollen, man muß auch tun.

Johann Wolfgang von Goethe

Meinen Eltern.

10-Jahres Epidemiologie der Infektiösen Endokarditis – Vergleich zwischen Histopathologie, Mikrobiologie und klinischer Präsentation

Hintergrund: Eine optimale Behandlung der infektiösen Endokarditis setzt einen frühen Erregernachweis, ein gründliches Wissen über die klinische Präsentation, das lokale Erregerspektrum, und die adäquate antimikrobielle und chirurgische Behandlung voraus.

Ziele: I) Erfassen von Epidemiologie und klinischem Auftreten von infektiöser Endokarditis (IE) bei Patienten mit Herzklappenoperationen wegen IE am Klinikum der Universität Regensburg. Vergleich dieser Daten mit anderen nationalen und internationalen Kohortenstudien. II) Vergleich von Nativklappenendokarditis (NVE) mit Prothesenklappenendokarditis (PVE) III) Korrelation von Keimart mit anatomischer Lage, klinischer Präsentation und histopathologischen Schadensmustern von betroffenen Herzklappen.

Methoden: In einer retrospektiven Studie wurden zwischen September 1994 und Februar 2005 alle 211 intraoperativ bestätigten Endokarditisepisoden (205 Patienten) am Klinikum der Universität Regensburg analysiert.

Ergebnisse: Eine NVE zeigte sich in 84%, eine PVE in 16% der Episoden. Ein alleiniger Aortenklappenbefall fand sich in 49%, ein alleiniger Mitralklappenbefall in 28%, ein kombinierter Aorten- und Mitralklappenbefall in 18%, ein Befall des rechten Herzens in 4%, und ein gleichzeitiger Befall des linken und des rechten Herzens in 1% der IE Episoden. *S. aureus* wurde in 20% der Fälle nachgewiesen, *S. viridans* in 14%, Enterokokken in 9.5%, Streptokokken außer *S. virdians* (SOTSV) in 8.5%, *S. epidermidis* in 6%, sonstige Keime in 9.5%, und Doppelinfektionen in 4%. Kulturnegative Endokarditis (CNE) trat in 32% der Episoden auf. In 38% aller Fälle lag begleitend eine Sepsis vor, in 34% traten Embolien auf. Die Letalität betrug 10% für die ersten 15 Tage und 14% für die ersten 30 Tage nach Operation. *S. aureus* präsentierte sich von allen Erregern mit dem höchsten Anteil an Sepsis (81%), septischen Streuherden (45%), Embolien (64%), cerebralen Embolien (45%) und wies unter allen Erregern die höchste Letalität (21%) auf. Enterokokken IE zeigte die höchste Abszessrate (60%) und betraf bevorzugt nur die Aortenklappe (70%). *S.*

viridans trat in 97% fast ausschließlich bei Nativklappen auf und hatte die höchste Perforationsrate (90%). Histopathologische Ergebnisse zeigten keine signifikante Korrelation mit den verursachenden Erregern.

Folgerungen: Mit Ausnahme eines relativ hohen Anteils an CNE zeigte sich die Epidemiologie der infektiösen Endokarditis in dieser Studie weitgehend übereinstimmend mit Resultaten aus vergleichbaren nationalen und internationalen Studien. Die Letalitätsraten in dieser Population lagen im Bereich von vergleichbaren Studien. Die Endokarditiden unterschieden sich deutlich in ihrem klinischen Erscheinungsbild, je nach verursachendem Erreger. Die Histopathologie der entfernten Klappen zeigte jedoch keine Keim-spezifischen Schadensmuster.
Aufgrund der Beobachtungen in dieser Untersuchung erscheint die histopathologische Aufarbeitung von Herzklappen nicht sinnvoll. Stattdessen sollte die mikrobiologische Diagnostik nicht nur Blutkulturen, sondern wann immer möglich auch Kulturen aus reseziertem Klappengewebe umfassen. Zudem sollten neue Techniken wie bakterielle PCR aus entferntem Klappenmaterial etabliert werden, was speziell für Endokarditisepisoden mit fehlendem Keimnachweis interessant erscheint.

Schlüsselwörter: Infektiöse Endokarditis, Epidemiologie, Erreger, Klappenersatz, Nativklappenendokarditis, Prothesenklappenendokarditis

10-Year Epidemiology of Infective Endocarditis – Correlations between Histopathology, Microbiology and Clinical Presentation

Background: Optimal management of IE depends on the early detection of IE-causing pathogens, knowledge of the clinical presentation of the local pathogen spectrum and appropriate antimicrobial and surgical therapy.

Objectives: I) To describe the epidemiology and clinical presentation of patients receiving heart valve surgery for infective endocarditis (IE), and to compare these data with national and international cohort studies. II) To correlate native valve endocarditis (NVE) episodes with prosthetic valve endocarditis (PVE) episodes. III) To correlate pathogens with anatomic locations, clinical findings and histopathologic damage patterns of affected heart valves.

Methods: 211 intraoperatively confirmed endocarditis episodes (in 205 patients) between September 1994 and February 2005 were reviewed. Data were extracted from surgical records, microbiology results, histopathology reports, in-house charts and medical charts of admitting hospitals, whatever appropriate.

Results: NVE was present in 84% and PVE in 16%. The aortic valve was affected in 49%, the mitral valve in 28%, the aortic and mitral valve in 18%, valves of the right heart in 4%, and both valves of the left and the right heart in 1% of all IE episodes. *S. aureus* accounted for 20%, *S. viridans* for 14%, Enterococci for 9.5%, Streptococci other than *S. virdians* (SOTSV) for 8.5%, *S. epidermidis* for 6%, miscellaneous pathogens for 9.5%, and mixed infections for 4%, respectively. Culture-negative endocarditis (CNE) was found in 32%. Sepsis was present in 38% and emboli occurred in 34% of all episodes. Mortality was 10% in a 15-day postoperative period and 14% in a 30-day period. *S. aureus* infections had high rates of sepsis (81%), septic foci (45%), embolic events (64%), cerebral-embolic events (45%), and a high 30-day mortality (21%). Infections by Enterococci showed the highest abscess rate (60%) and predominately affected the aortic valve (70%). *S. viridans* infections almost exclusively affected native valves (97%) and had the highest perforation rate (90%). Histopathological findings did not show any significant correlations with pathogens.

Conclusions: Results on IE epidemiology confirmed findings of previous studies except for a higher CNE infection rate, which differed remarkably from rates found in other investigations. Mortality in this cohort was similar to that in previous studies. The clinical presentation of IE differed remarkably, depending on the pathogen. In contrast, histopathological findings did not reveal pathogen-specific damage patterns and added little information overall. According to the results of this study, histopathological workup of resected heart valves can be omitted. Instead, in addition to blood cultures, microbiological testing should be complemented with cultures of resected valve tissue whenever possible. Furthermore, new techniques such as bacterial PCR on resected valve tissue should be established as routine diagnostic tool and might be especially helpful in culture-negative IE.

Keywords: infective endocarditis, epidemiology, pathogen, valve replacement, native valve endocarditis, prosthetic valve endocarditis, valvular damage, damage pattern

Introduction:

Infective endocarditis (IE) is a bacterial or fungal infection of the inner structures of the heart, most often involving heart valves of the left heart, rarely of the right heart or both sides. Infection restricted to the endocardium without involvement of heart valve structures is uncommon. Damage of the heart valves is a major complication and worsens the prognosis of IE. Leaflet perforations, chordae tendineae ruptures and annulus dehiscences lead to valve insufficiencies and valve prolapses with detrimental effects on the circulation. Vegetations and abscesses bear the risk of thrombus generation, which may cause embolic events and metastatic spread of the infection. The incidence of IE has considerably decreased in western countries and is nowadays estimated to be 20-70 cases per million inhabitants[1-3].

The management of IE requires knowledge and expertise, and it is a challenge to decrease mortality below today's 10-18%[1, 4, 5]. Multiple reasons are responsible for this lack of progress.

The aging of western societies and medical treatment provides an increasing number of multimorbid and immunocompromised patients. Temporal trends show increasing intravenous drug abuse, decreasing rheumatic endocarditis, an increase in antimicrobial resistance, and an increasing use of invasive diagnostic and therapeutic procedures[6-9]. As a consequence, the spectrum of organisms causing endocarditis currently undergoes changes, which has implications on IE treatment.

Optimal management of IE depends on accurate knowledge of the clinical presentation[10], the local pathogen spectrum, prompt detection of IE-causing pathogens, and adequate antimicrobial and appropriate surgical therapy[11].

This study adds information on the epidemiology and clinical presentation of IE for the region of Eastern Bavaria, and the data should be generalizable for other western countries[5, 11, 12]. Data from patients receiving heart valve surgery for IE at the Regensburg University Medical Center were collected, analysed and compared to published data. The aim of this study was to deliniate damage patterns and differences in clinical presentation associated with various pathogens and to evaluate the role of pre- and postoperative diagnostic procedures. Therefore, identified pathogens were correlated with anatomic locations, clinical findings and histopathologic damage patterns of affected heart valves

Materials and Methods:

Study Design:

This retrospective single center study was performed at the Div. of Infectious Diseases, Dept. of Internal Medicine I in cooperation with the Dept. of Cardiothoracic and Vascular Surgery at Regensburg University Medical Center (tertiary university hospital). Data from 205 caucasian patients from the region of Eastern Bavaria, who underwent heart surgery for IE were analysed. Patients were diagnosed with IE using the modified Duke criteria for the diagnosis of infective endocarditis[13, 14]. The period of investigation comprised more than 10 years (September 1994 to February 2005). Data were extracted from the in-house information system of the Department of Cardiothoracic and Vascular Surgery. Only patients with intraoperatively confirmed IE were included into the study. Data were complemented with microbiological and histopathologic reports as well as information from in-house charts and medical charts of admitting hospitals, whatever appropriate. Extracted data were thoroughly reviewed and analyzed by two independent investigators (F.Z., F.A.) in order to prevent systematic and observational errors. Due to incomplete or inconsistent documentation, five patients were excluded from the study.

Data Collection:

Surgical records and medical charts were available for all cases, and provided basic information on sex, age, type of endocarditis (NVE vs PVE), location of IE (affected valves), type of valve surgery (replacement vs reconstruction), and type of valve replacement (biological vs mechanical), if applicable. Details concerning valve condition and valvular damage were collected for each patient, such as damage on/below/above valve level, bicuspid valve, valve insufficiency, valve stenosis, valve prolapse, perforation of valvular cusps, abscesses, vegetations, vegetation thrombi, and other types of damage.

In-house charts and medical charts of admitting hospitals were screened for information on presence of diabetes mellitus, sepsis (including sepsis, severe sepsis and septic shock episodes), septic metastatic foci, embolic events, relevant comorbidities, diagnostic procedures (echocardiography, microbiology, histopathology, intraoperative diagnosis), 15-, 30- and 90-day mortality, and durations of intensive care unit (ICU) / intermediate care unit (IMC) and hospital stay.

Histopathologic examination was available in 89% of all IE episodes (NVE: 95.5%; PVE: 56%). Histopathology reports offered exact endocarditis diagnoses and added information on valvular damage patterns of the resected tissue: type and location of valvular damage, vegetations, bacterial colonization, calcifications, fibrin deposits, ulcerations, necrosis, presence of lymphocytes or granulocytes, abscesses, vegetation thrombi, perforation of valvular cusps and other types of damages.

Data on pathogens were extracted from the database of the Institute of Microbiology and Hygiene and from reports of admitting hospitals. Type of specimen and isolated pathogens were recorded. Blood cultures were done in all episodes. Additionally, in 5% of the episodes resected tissue, and in 1% thrombotic material or central venous catheters were sent for culture. Standard variables were defined for all parameters, and combined data were thoroughly reviewed and crosschecked.

Statistical Analysis:

Data were entered in Microsoft Excel 2000 9.0.2812. (Microsoft Corporation ©1985-1999), and subsequently transferrred into SPSS 12.0.0. (SPSS Inc. ©1989-2003) for statistical calculation. Descriptive data were extracted and variables were compared using the Chi-Square Test, Likelihood Ratio and Fisher's Exact Test, when appropriate. For statistical reasons, eight episodes with two detected pathogens (mixed infections) were not included in the correlation calculations. A p-value of 0.05 was considered statistically significant.

Results:

Patient characteristics and diagnostic procedures

205 patients underwent 211 endocarditis episodes in the observation period between September 1994 and February 2005. Surgery was performed on 252 heart valves (see Table 1). 84% of the IE episodes involved native valves (NVE) and 16% prosthetic valves (PVE). Echocardiography was documented in 98% of all cases. In detail, transesophageal echocardiography (TEE) was applied in 25%, transthoracal echocardiography (TTE) in 1%, and transesophageal and transthoracal echocardiography (TEE+TTE) in 25% of all episodes. Echocardiography was documented, but not further specified in 47%. In 2% application of echocardiography was not documented. In 95% of the IE episodes this diagnostic method allowed to make a provisional diagnosis of IE, either by showing valvular perforation, valve prolapse, valve insufficiency, dehiscence of the valvular ring, regurgitation, vegetations or vegetation thrombi.

Patient characteristics are summarized in table 1. Median age at the time of surgery was 61 years (range 22 to 80, mean: 58). PVE and NVE patients had similar median age and sex ratio. Male patients accounted for 75%, female for 25%. 24% of all patients had diabetes mellitus as a risk factor. In 38% of all episodes, patients met sepsis criteria at the time of surgery with no significant difference between NVE and PVE patients (39.5% vs 32%, $p>0.4$). Septic metastatic foci were present in 23% of all cases. Embolic events were documented in 34% of all IE episodes.

Valves affected with IE

Affected valves were located in the left heart in 95%, in the right heart in 4%, and in the left and the right heart in 1%. The distribution of infected valves was as follows: aortic valve 49%, mitral valve 28%, aortic and mitral valve 18%, tricuspid valve 3%, pulmonary valve 1%, and combined affection of valves in the left and the right heart 1%. In 81% of all episodes one valve was the only site of IE. Multiple valves were significantly more often affected in NVE than in PVE (21.5% vs 6%, $p<0.04$). Endocarditis was present at the aortic valve only at a significantly higher rate in the PVE than in the NVE group (70.5% vs 44.5%, $p<0.01$). 91.5% of all affected valves showed insufficiencies. NVE was significantly more often associated with

insufficiency than PVE (95% vs 76.5%, p<0.01). Stenosis was present in 13% of all episodes. 8.5% of all native aortic valve IE episodes occurred at a bicuspid valve.

Surgical Procedures

83% of all surgical procedures were primary interventions, 17% reinterventions. 97% of the reinterventions were performed in the PVE group. Single valve surgery was performed in 90%, and multiple valve surgery in 9% of all episodes, the latter in NVE cases only. In PVE episodes mechanical valves were implanted in 59%, biological valves in 38%, and valves were reconstructed in 3%. In NVE episodes mechanical valves were implanted in 58%, biological valves in 16%, and valve reconstruction was done in 15%. In 11% of the NVE episodes multiple surgery was performed. In two NVE episodes (1%) the type of valve replacement could not be determined retrospectively.

Histopathology

Surgical and histopathological records documented perforation of valvular cusps in 71% of all episodes. In 30% of all episodes valve chordae were ruptured, resulting in valve prolapses. Valvular damages not further specified occurred in 21% of the episodes. Abscesses at the valve ring were present in 31% of all episodes. PVE showed significantly more abscesses than NVE (59% vs 26%, p<0.01). Vegetations were present in 88%, vegetation thrombi in 55% and calcifications in 84%. Valves showed fibrin deposits in 84%, ulcerations in 33% and necrotic areas in 32%. Bacterial colonization was present in 25% and lymphocytes in 23%. Granulocytes were significantly more often present in the NVE group than in the PVE group (63% vs 32%, p<0.01).

Outcome

Median time of IMC or ICU stay was 4 postoperative days (mean: 7 days), and median time of hospital stay 13 days (mean: 15 days).

Mortality after cardiac surgery was 10% for a 15-day period, 14% for a 30-day period, and 17% for a 90-day period, respectively, 30-day mortality decreased from 17% between 1994 and 1999 to 12% between 2000 and 2005 (p>0.2). Median time to death in the 30-day period was 7 days after surgery (mean: 9 days). 30-day mortality of patients younger than 60, between 60 and 70, and older than 70 was 8.5%, 18%

and 22% respectively. The difference in mortality between patients younger than 60 and those older than 70 years was statistically significant (p=0.04). Gender did not influence mortality. 15-day mortality of patients with NVE and PVE was 8.5% and 21% (p=0.052). 30-day and 90-day mortality was significantly higher in PVE than in NVE (11% vs 29%, p<0.01, and 14% vs 32%, p<0.01, respectively). Patients who received a single valve replacement with a bioprosthesis had a significantly higher 30-day mortality compared to patients who received a single valve replacement with a mechanical valve (29% vs 14%, p<0.03). Involvement of multiple valves in the IE episode, diabetes, sepsis, septic metastatic foci, embolic events or cerebral-embolic events were not associated with higher mortality. Furthermore, histopathological variables (presence of calcification, fibrin deposit, ulcerations, necrosis, bacterial colonization, vegetation, abscesses, valvular perforation, insufficiency or prolapse) showed no association with mortality. However, presence of vegetation thrombi on the valves was significantly associated with a higher 30-day mortality rate (19% vs 8%, p<0.03).

Microbiologic results and correlations to other parameters

Microbiologic identification of causative pathogens was successful in 68% of all IE episodes (see Table 2). Blood cultures were drawn in all IE episodes. Resected valve tissue was sent for culture in 11 episodes (5%), of which 10 episodes led to the identification of the IE-causing pathogen. In two episodes the culturing of thrombotic material and a pacer wire led to positve results.

S. aureus was responsible for 20% of all IE episodes, *S. viridans* for 14%, Enterococci for 9.5%, Streptococci other than S. virdians for 8.5%, *S. epidermidis* for 6% and miscellaneous pathogens for 6%. In another 8 episodes (4%) two pathogens were isolated. 32% of the episodes were culture negative, two episodes of these (1%) were presumably due to rheumatic endocarditis. *Viridans streptococci* could be divided into four groups: unspecified *S. viridans spp.* (5%), *S. mitis* (4%), *S. sanguis* (3%) and *S. anginosus* (formerly *"S. milleri"*; 2%). Enterococci were differentiated into *Enterococcus faecalis* (6%), unspecified *Enterococcus* spp. (2.5%) and *Enterococcus faecium* (1%). Streptococci other than *S. viridans* (SOTSV) comprised *S. bovis* (4%), *S. agalactiae* (1%), *S. pneumoniae* (1%), and several unspecified Streptococci: *S. haemolyticus* (group C, 1%), *ß-haemolyzing Streptococcus* (0.5%), *S. equisimilis* (0.5%) and *S. anhaemolyticus* (0.5%).

Miscellaneous pathogens represented a heterogenous group of 11 different pathogens (see Table 2): *Escherichia coli* (1%), *Aerococcus viridans* (0.5%), *Candida albicans* (0.5%), *Enterobacter cloacae* (0.5%), *Gemella morbillorum* (0.5%), *Propionibacterium acne* (0.5%), *Staphylococcus caprae* (0.5%), *Staphylococcus xylosus* (0.5%), *Stenotrophomonas maltophilia* (0.5%), one unspecified *Staphylococcus spp.* (0.5%) and one unspecified Gram-positive Coccus (0.5%).

Pathogen spectra differed between NVE and PVE episodes (see Table 1). *S. aureus* was the most prevalent pathogen in the NVE group (21.5%). Among all episodes, *S. aureus* affected the mitral valve at the highest rate (40.5%). There were significant lower rates of mitral valve affection by SOTSV (6%; $p<0.01$), miscellaneous pathogens (8%, $p<0.03$) and Enterococci (10%, $p<0.02$). Patients with *S. aureus* IE showed a significantly higher perioperative sepsis rate (81%) than patients with IE due to other pathogens such as Enterococci (55%, $p<0.04$), *S. epidermidis* (46%, $p<0.02$), SOTSV (50%, $p<0.02$), *S. viridans* (27%, $p<0.01$), miscellaneous pathogens (17%, $p<0.01$), and CNE (13%, $p<0.01$). *S. aureus* IE showed a significantly higher rate of embolic events (64%) than IE episodes by Enterococci (10%, $p<0.01$), *S. epidermidis* (31%, $p<0.04$), *S. viridans* (33%, $p=0.01$), CNE (19%, $p<0.01$), or miscellaneous pathogens (17%, $p<0.01$). Only patients with IE due to SOTSV had a similar rate of embolic events (67%). IE due to *S. aureus* also caused a higher rate of cerebral-embolic events (45%) than IE due to other pathogens; *S. viridans* (17%, $p<0.02$), miscellaneous pathogens (8%, $p<0.02$) and CNE (6%, $p<0.01$) showed significantly less cerebral-embolic events. Septic metastatic foci occurred in 45% of the episodes caused by *S. aureus*, which was of similar magnitude as in episodes caused by Enterococci and SOTSV (45% and 39%). IE episodes due to *S. viridans* (20%, $p<0.03$), miscellaneous pathogens (8%, $p<0.02$), and CNE (6%, $p<0.01$) showed significantly less septic metastatic foci. These observations are in agreement with histopathological results, showing *S. aureus* IE to have the highest rate of vegetation thrombi (74%). In contrast, *S. aureus* IE showed calcifications in the second lowest rate (72%), IE episodes due to *S. viridans* and CNE had a significantly higher calcification rate (93%, $p<0.03$, and 95%, $p<0.01$, respectively). SOTSV IE episodes had the lowest calcification rate, not significantly different from episodes caused by *S. aureus*. 30-day mortality rate was higher in *S. aureus* IE episodes (21%) than in episodes caused by other pathogens, but the difference did not reach statistical significance.

S. epidermidis was associated with PVE in 46% of the IE episodes with this pathogen, and represented the leading pathogen in the PVE group (17.5%). *S. epidermidis* IE involved most often only a single valve (92%). Valve insufficiency was present in 69%, which represented the lowest prevalvence of all pathogens, and was significant lower than in IE caused by *S. viridans* (100%, p=0.001), SOTSV (100%, p<0.01), Enterococci (100%, p<0.01), and *S. aureus* (93%, p<0.04). In no episode with this pathogen valvular stenosis was seen.

S. viridans appeared significantly more often in NVE than in PVE (16% vs 3%, p<0.02). *S. viridans* showed the highest valve perforation rate of all pathogens (90%), which was significantly higher than in IE caused by *S. epidermidis* (54%, p=0.01) or CNE (54%, p<0.01). *S. viridans* IE also showed the highest prolapse rate (47%), although this was not significantly different from IE caused by other pathogens.

Enterococci appeared at similar rates in NVE and PVE (10% and 9%, respectively). In 70% of IE episodes by Enterococci, only the aortic valve was affected. This was significantly higher than in IE caused by *S. aureus* (40.5%, p<0.01) or *S. viridans* (37%, p<0.03). Patients with Enterococcal IE showed the second highest sepsis rate (55%), significantly higher than in IE caused by *S. viridans* (27%, p<0.05), miscellaneous pathogens (17%, p<0.03) or CNE (13%, p<0.01). Enterococci caused the lowest rate of embolic events (10%) or cerebral-embolic events (0%). Both of these rates were lower than in IE caused by SOTSV (67%, p<0.01, and 28%, p<0.01, respectively) or *S. aureus* (64%, p<0.01, and 45%, p<0.01, respectively), even though vegetations at the valves were present in all Enterococcal IE cases. Prevalvence of vegetations was not significantly different between the different pathogen groups, except for patients with IE caused by CNE; those showed significantly less vegetations (71%, p<0.01). Local valve or valvular ring abscesses occurred in 60% in Enterococcal IE, which was the highest rate compared to IE episodes caused by other pathogens. *S. aureus* (33%, p<0.05) and CNE cases (18%, p<0.01) presented significantly less often with local abscesses.

SOTSV caused NVE and PVE episodes similarly often, in 8.5% and 9%, respectively. In this group the mitral valve was involved in only 6%, a much lower rate than seen in IE caused by other pathogens. CNE and *S. aureus* had significantly higher rates of mitral valve involvement (35.5%, p<0.02, and 40.5%, p<0.01, respectively). Embolic events happened more often in SOTSV IE (67%) than in all other IE episodes. Only *S. aureus* IE showed an embolic event rate of similar

magnitude (64%). IE caused by other pathogens had a significantly lower embolic event rate: *S. viridans* (33%, p<0.03), *S. epidermidis* (31%, p<0.05), CNE (19%, p<0.01), miscellaneous pathogens (17%, p<0.01) and Enterococci (10%, p<0.001). SOTSV IE caused the lowest calcification rate (53%) of all groups. Enterococci, *S. viridans* and CNE had significantly more calcifications (85%, p<0.04; and 93%, p<0.01; and 95%, p<0.01, respectively).

Pathogens classified into the heterogeneous group miscellaneous pathogens were found in similar freqency in NVE and PVE episodes (5% vs 9%). More than one valve was affected by these pathogens in the highest rate of all pathogen groups (58%), significantly higher than in IE episodes by *S. aureus* (12%, p<0.03), CNE (12%, p=0.02) or *S. epidermidis* (8%, p=0.04). Patients with miscellaneous pathogens had low rates of sepsis (17%), septic metastatic foci (8%), embolic events (17%) and cerebral-embolic events (8%). Moreover, IE by these pathogens were associated with low rates of local abscesses (25%) and valve prolapses (17%), but the differences were not significant. 30-day mortality in IE due to miscellaneous pathogens was very low (8%), but not significantly different to IE due to other pathogens.

CNE occurred in similar rates in NVE and PVE episodes (32% vs 35%, respectively). Patients with CNE met sepsis criteria in only 13% of the cases. This was significantly lower than in IE caused by *S. epidermidis* (46%, p<0.02), SOTSV (50%, p<0.01), Enterococci (55%, p<0.01) and *S. aureus* (81%, p<0.01). CNE showed the lowest rate of septic metastatic foci (6%), significantly less than in IE due to *S. viridans* (20%, p<0.05), SOTSV (39%, p<0.01), Enterococci (45%, p<0.01), and *S. aureus* (45%, p<0.01). In CNE episodes, valvular vegetations were present in a lower rate (71%) than in other IE cases. Vegetations were significantly more prevalent in IE due to Enterococci (100%, p<0.01), *S. aureus* (98%, p<0.01), SOTSV (94%, p<0.02), and *S. viridans* (93%, p<0.02). In contrast, CNE presented with the highest rate of valvular stenosis (22%).

According to histopathology results, valve calcifications were present in 95% of the CNE episodes, which was the highest rate among all IE. *S. aureus* IE (72%, p<0.01) and SOTSV IE (53%, p<0.01) had significantly lower calcification rates. Patients with CNE showed low rates of fibrin deposit (32%), ulcerations (18%), necrosis (14.5%), bacterial colonization (13%) and granulocyte infiltrations (45%). IE episodes caused by Enterococci, SOTSV, and miscellaneous pathogens had significantly higher rates

of fibrin deposit (61%, p<0.03; and 65%, p<0.02; and 70%, p<0.03) than IE episodes due to CNE. Similarly, patients with IE episodes due to *S. aureus*, Enterococci, and SOTSV developed ulcerations at a significant higher percentage (39%, p<0.03; and 44%, p<0.03; and 47%, p<0.02, respectively) than patients with IE due to CNE. Necrosis was significantly more often present in IE caused by SOTSV (41%, p<0.03), miscellaneous pathogens (44%, p<0.05), *S. aureus* (44%, p<0.01), and Enterococci (50%, p<0.01) than in CNE. Furthermore, CNE showed significantly less bacterial colonization than IE caused by *Stahylococcus aureus* (30%, p=0.04) and miscellaneous pathogens (67%, p<0.01). Granulocyte infiltrations into the valvular cusps were significantly more often associated with Enterococci (78%, p<0.02), *S. aureus* (81%, p<0.01), and SOTSV (88%, p<0.01) than with CNE.

Discussion:

This retrospective 10-year study was undertaken at a German university hospital. The epidemiology and clinical presentation of patients receiving heart valve surgery for IE was described, and NVE was compared with PVE. The aim of this study was to delineate damage patterns and differences in clinical presentation associated with various pathogens and to evaluate the role of pre- and postoperative diagnostic procedures.

The proportion of NVE in our cohort was high, but still in accordance with recently published international data[11-13]. As expected, IE in the population studied mainly involved valves of the left heart. The distribution of infected valves in NVE and PVE patients was similar to results found in several other studies on IE[15-20].

The range and distribution of the operative procedures performed in this series was similar to published studies, too. According to the literature, most centers preferred the insertion of mechanical valves, but with a wide range between 56% and 97%[16, 21-25].

Characteristics of our study population were largely comparable to those found in the literature. Male gender clearly predominated in all groups (total, NVE, PVE). PVE patients tended to be older than NVE patients (mean age: 62 vs 57 years). In all groups patients' mean age was in the upper range of similar previously published studies[22, 26-28]. Over the past decade, mean age seems to have increased in patients with operated IE of all causes.

Echocardiography was performed in almost all episodes in this study. Unfortunately the type of echocardiography could not be further specified in 50% of the episodes. This is due to the retrospective nature of this study with its inherent problems of unstandardized documentation. In 95% of the episodes this diagnostic method allowed a provisional diagnosis of IE, which emphasizes the role and importance of echocardiography in the diagnosis of IE, as has been acknowledged by the important role of echocardiography in the revised Duke criteria for the diagnosis of IE[13].

In this study population diabetes mellitus was prevalent at a relatively high rate, which may be due to the high mean age of our cohort. Published studies report widely varying diabetes rates of 6.5% to 36%[24, 29, 30]. According to the current literature, diabetes mellitus is seen as an independent risk factor for a poor prognosis in IE, but this could not be confirmed by our data[31-33]. Bicuspid aortic valves were

reported in 9% to 17% in other series of operated NVE[12, 17, 28, 34]. The proportion of bicuspid aortic valves in this series was low. Perioperative sepsis, including sepsis, severe sepsis and septic shock episodes, was present in a relatively high percentage in this series, without significant difference between NVE and PVE patients. Only Tornos found a similar high sepsis rate of 40% in a mixed NVE-PVE-cohort, and Balasubramanian reported a sepsis rate of 33% among operated NVE patients[35, 36]. Other studies reported lower rates of sepsis, e.g. 9% in a mixed NVE-PVE-population, 18% among operated NVE patients, and 19% in operated PVE patients[21, 25, 37*].

The rates of embolic events and cerebral-embolic events in our study are similar to results found in a large French cohort study[27]. According to the current literature embolic events occur in 29.5% to 40% of the IE episodes, and cerebral-embolic events in 13% to 20%[16, 18, 19, 24, 25, 36, 38]. Like in most of these studies, also in our population embolic events tended to occur more often in NVE than in PVE patients.

Pathogen spectra for NVE and PVE episodes in this study are similar to spectra observed in other recent comparable investigations[36, 38]. In NVE episodes *S. aureus* turned out to be the pathogen detected most frequently, and in PVE episodes this was *S. epidermidis*. This is in contrast to older literature, which reported *S. viridans* as the predominating pathogen[18, 25]. The epidemiology of pathogens causing IE is obviously changing, and this study confirms that *S. aureus* has now become the most prevalent pathogen in operated NVE.

Notably, no HACEK-pathogens were detected in this cohort, although the literature suggests HACEK-prevalences of up to 6%[12, 21, 29, 39, 40]. At the same time, the CNE rate in our study was relatively high, both in NVE and PVE. Several studies including medical and surgical patients showed widely varying CNE rates between 5.5% and 46%[16, 23-25, 35]. Recently, a large international study investigating the benefit of early surgical intervention in 610 NVE episodes found a very low CNE rate of only 6%[26]. Reasons for these varying CNE rates may be due to the different inclusion criteria in the various studies. Epidemiological investigations on NVE suggest CNE rates between 10% and 12%[20, 26, 36, 38, 39], whereas surgical case series investigating PVE report CNE rates of 21% to 33%[18, 23, 37, 41]. The literature on PVE epidemiology shows rates between 10% and 35%[20, 36, 38, 39]. In our study, the high CNE rate and the absence of HACEK-pathogens may be due to missing standardization of

* Authors did not differ between sepsis, severe sepsis or septic shock

microbiological diagnostic methods (i.e. application errors, different blood culture systems, too short incubation time), the retrospective nature of this study, and possibly premature initiation of antibiotic treatment at admitting hospitals in many cases. Correct and standardized microbiological testing might have revealed HACEK-pathogens and might have also resulted in a lower CNE rate. In our study, culturing of resected valve tissue led to the identification of IE-causing pathogens in most of the cases, when applied. In contrast, histopathological results of resected heart valves did not reveal macroscopic or microscopic pathogen-specific damage patterns that allowed to conclude on possible causative pathogens. Lepidi[42] and Greub[43] stated that valve histology remained the gold standard for the diagnosis of IE. The current German S2 Guideline on diagnosis and therapy of IE[44] also recommends the implementation of histopathological examination, especially if microbiological culturing, clinical profile and imaging methods do not show clear results. However, our findings suggest that histopathologic processing of resected valve tissue is not necessary. Instead, in addition to blood cultures, microbiological testing should be augmented with cultures of resected valve tissue whenever possible. Furthermore, bacterial PCR should be performed on resected valve tissue. Several authors agree that PCR is a valuable supplement to the current standard workup of resected valve tissue[45, 46]. PCR is not only more sensitive, specific and rapid than valve culture, but also allows identification of the full spectrum of IE causing pathogens, especially in CNE episodes [10, 46, 47]. Some authors even recommend to introduce PCR as a new Duke criterion for the diagnosis of IE[45, 48, 49].
Episodes without detection of pathogens proved to be less severe compared to culture-positive IE episodes in this study. The rates of perioperative sepsis, septic metastatic foci, local abscesses, vegetation thrombi, embolic events, cerebral-embolic events and valve perforations were lowest in CNE episodes. Histopathological findings confirmed these findings by showing low rates of fibrin deposits, ulcerations, necrosis, bacterial colonization and granulocyte infiltrations. On the other hand calcification and stenosis was more prevalent in CNE than in culture-positive IE, which may point towards a longer disease course in such cases with less virulent pathogens. Consequently, 30-day mortality in patients with CNE was only 13%. A recent Swedish study reported a similar low mortality rate of 5% in CNE cases[50]. Similarly, Marks showed a significant lower mortality rate of CNE patients compared to patients with culture-positive IE[51]. In contrast, Zamorano reported that

CNE-patients had a higher frequency of valve rupture, valve perforation and heart failure, and concluded that their prognosis was worse than in patients with culture-positive IE[52]. However, the mortality rate in his study did not differ significantly between culture-negative and culture-positive IE. Hoen also found no remarkable difference between culture-negative and culture-positive IE cases regarding patient characteristics, clinical features, and outcome [53].

S. epidermidis was the pathogen isolated most often in PVE episodes. It was associated with a high rate of single valve affection, and a preference for the aortic valve. These results are in agreement with results found in the current literature[20, 29, 39, 54]. Low perforation, stenosis and insufficiency rates in *S. epidermidis* IE in our cohort may be a consequence of the high proportion of PVE. Most of the inserted prostheses were robust and durable mechanical valves, which rarely break down. Episodes caused by *S. epidermidis* presented with less embolic events than episodes caused by *S. aureus*. This is in agreement with findings by Chu, who noted a significant lower rate of embolic and cerebral-embolic events in patients with coagulase negative staphylococci NVE compared to patients with *S. aureus* NVE[55, 56]. Similarly, Lalani found that patients with coagulase negative staphylococci PVE suffered less embolic events than patients with other forms of IE, although they had vegetations in similar frequency[57].

Valvular perforations, prolapses and insufficiencies were present mainly in the NVE group, likely because native valves are more vulnerable than mechanical prostheses[58]. IE caused by *S. viridans* showed the highest valve perforation rate. To some extent, this may be due to the high proportion of NVE cases in the *S. viridans* group. Contradictory results on this issue can be found in the literature. Lopez reported similar findings, and showed that prosthetic valves were less frequently affected in *S. viridans* IE episodes compared to IE of other origin[59]. Low mortality, sepsis and embolism rates in combination with a high calcification rate found in our study support recent observations considering *S. viridans* a less agressive pathogen with lower complication rates and mortality, and a relatively good prognosis[59-61].

In contrast, histologic findings in the SOTSV group showed the lowest calcification rate, whereas lymphocytic and granulocytic infiltrates were found more frequently, indicating a more vigorous immune response to these pathogens. These results were signifcantly different from the findings in *S. viridans*-infected valves or in CNE.

SOTSV IE was associated with the highest rate of embolic events, only IE due to *S. aureus* showed embolic events in similar frequency. Despite this, 30-day mortality of SOTSV IE was relatively low, presumably due to a good response to antibiotic therapy.

Cardiac abscesses were observed at a higher rate in PVE than in NVE in this study, but such local abscesses did not represent a risk factor for mortality. Enterococci presented with the highest abscess rate of all pathogens. Anderson found similar results and concluded that enterococcal PVE had a higher likelihood of developing intracardiac abcesses[62]. However, Anderson's and several other studies ranged between 5% and 10% only[62-64]. The higher abscess rate in this investigation may be explained by the surgical patient population studied. The above mentioned trials also included medical patients, which may explain the lower abscess rates.

Enterococci were associated with a relatively high sepsis rate, and a preverence for the affection of the aortic valve only. This observation is in contradiction to results found in other studies, which reported a single affection of the aortic valve in only 34% to 49%[64, 65]. Still, McDonald found that in enterococcal endocarditis vegetations were found predominately at the aortic valve and less likely at the mitral valve compared to IE due to other pathogens[63]. In contrast to the high abscess and sepsis rate, enterococcal IE was associated with the lowest rate of embolic events and did not show any cerebral-embolic events. Other studies are in line with these findings, and also showed low rates of embolic events in enterococcal IE, ranging between 26% and 29%, and rates of cerebral-embolic events between 12% and 21%[62, 63, 66]. McDonald concluded that Enterococci cause emboli less often than *S. aureus* [63].

In this investigation, *S. aureus* IE had a significantly higher rate of embolic events than IE due to most other pathogens, and significantly higher rates of cerebral-embolic events than IE due to *S. viridans*, CNE or miscellaneous pathogens. Fowler and Miro also reported a significantly higher rate of embolic events including a higher rate of cerebral-embolic events in *S. aureus* IE[67, 68]. Furthermore, *S. aureus* IE was associated with a significantly higher perioperative sepsis rate than in IE due to any other pathogen. Septic metastatic foci were also seen most frequently in *S. aureus* IE. This confirms results of previous studies, which reported significantly higher rates of severe sepsis and septic shock among patients with *S. aureus* IE[69-71]. The higher complication rates of *S. aureus* IE are reflected in the highest 30-day

mortality rate among all pathogen groups in this study. Two large international studies reported mortality rates for *S. aureus* IE of similar magnitude (22% and 20%, respectively)[67, 68]. In these studies, the mortality difference of *S. aureus* IE compared to IE due to other pathogens was significant. In this investigation, however, the difference did not reach significance, possibly due to lower power.

Mortality in our cohort was significantly higher in PVE patients for the 30-day and 90-day period, but not for the 15-day period. In comparable studies 30-day mortality rates ranged between 4% and 19.5% for NVE patients, and between 15% and 36% in PVE patients[16, 17, 20-23, 29, 38]. Comparison of 30-day mortality rates for the periods between 1994 and 1999 and between 2000 and 2005 showed a non-significant trend towards lower mortality rates. Patients who received biological valves had a higher 30-day mortality than patients who received mechanical valves. One of the reasons for this phenomenon might be the higher age of the patients who received bio-prostheses. Similar findings were reported by Hammermeister and Brown, who reported higher mean ages and mortality rates among patients who had received bio-prostheses for valve replacement after IE compared to patients with mechanical valve replacement[72, 73]. Lund and Khan only found significantly different mean ages, but similar mortality rates for patients with biological and mechanical valve replacement after IE[74, 75]. In the literature age over 70 years, presence of annular abscesses, severe sepsis or septic shock, diabetes mellitus, PVE, heart failure, *S. aureus*, cerebral embolization and IE at more than one valve are considered independent predictors for hospital mortality: [18, 22, 23, 25, 38, 40, 76]. This study confirms some of these predictive parameters. In the cohort investigated patients older than 70 years were at higher risk for mortality. Furthermore, patients with PVE had a higher mortality rate than patients with NVE, and patients with vegetation thrombi present at the infected valves were found to have a higher mortality rate, too.
In conclusion, this study describing the epidemiology of IE at a German tertiary center confirms many findings of previous investigations. Although a relatively high proportion of patients suffered from sepsis and embolic events the mortality rate was similar to those in other national and international studies. The high rate of CNE was most likely due to missing standardization of microbiological diagnostic methods, the retrospective nature of this investigation, and premature initiation of antibiotic treatment at admitting hospitals in many cases. Some IE pathogens were found to be associated with a characteristic clinical presentation, e.g. *S. aureus* with a high rate

of sepsis and septic embolic events, Enterococci with a high rate of annular abscesses, and *Viridans streptococci* with a high rate of valve perforations. Such associations may allow a first estimate of the causative pathogen, but the associations are too weak for clinical decision making.

In contrast to the clinical findings, results of histopathologic examinations did not reveal pathogen-specific damage patterns in this investigation and added little information overall. Therefore, histopathologic workup of resected heart valves can be omitted. Instead, in addition to blood cultures, microbiological testing should be complemented with cultures of resected valve tissue whenever possible. Furthermore, new techniques such as bacterial PCR from resected valve tissue should be established as routine diagnostic tool and might be especially helpful in culture-negative IE.

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Abbreviations

av only	aortic valve affected only
av & mv	aortic and mitral valve affected
CNE	Culture-negative Endocarditis
HACEK	Haemophilus species, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Klingella species
IE	infective endocarditis
ICU	Intensive Care Unit
IMC	Intermediate Care Unit
my only	mitral valve affected only
MRI	Magnetic Resonance Imaging
ns	no significance
NVE	native valve endocarditis
pv/tv only	pulmonary or tricuspid valve affected only
PCR	Polymerase Chain Reaction
PVE	prosthetic valve endocarditis
SOTSV	Streptococci other than *S. viridans*
TEE	Transesophageal Echocardiography
TTE	Transthoracal Echocardiography

Tables

	NVE	PVE	Total	NVE vs PVE	Correlation with 30-day Mortality
Number of episodes	84% (177)	16% (34)	100% (211; in 205 patients)	-	-
Sex: male / female	75% / 25%	76.5% / 23.5%	75% / 25%	-	ns (p>0.4)
Median (mean; range) age (in years)	57 (60; 22-80)	62 (66; 24-79)	61 (58; 22-80)	-	-
age<60y vs age>70y	77% (83) / 23% (25)	50% (11) / 50% (11)	72% (94) / 28% (36)	-	**p=0.01**
Predisposing Factors					
bicuspid aortic valve	8.5% (15)	-	7% (15)	-	ns (p>0.1)
diabetes mellitus	23% (40)	32% (11)	24% (51)	ns[1] (p>0.3)	ns (p>0.9)
sepsis	39.5% (70)	32% (11)	38% (81)	ns (p>0.4)	ns (p>0.06)
septic metastatic foci	25% (45)	12% (4)	23% (49)	ns (p>0.1)	ns (p>0.9)
Applied diagnostic methods					
echocardiography[2]	97% (172)	100% (34)	98% (206)	-	-
blood culture	100% (177)	100% (34)	100% (211)	-	-
intraoperative documentation	100% (177)	100% (34)	100% (211)	-	-
histopathology results	95.5% (169)	56% (19)	89% (188)	-	-
Type of surgery					
single valve surgery	**88% (156)**	**100% (34)**	**90% (190)**	-	ns (p>0.1)
bioprothesis	16% (28)	38% (13)	19% (41)	-	-
mechanical prosthesis	58% (102)	59% (20)	58% (122)	-	-
reconstruction of valve	15% (26)	3% (1)	13% (27)	-	-
multiple valve surgery (2 or more valves)	**11% (19)**	**-**	**9% (19)**	-	ns (p>0.1)
reconstruction + bioprothesis	3.5% (6)	-	3% (6)	-	-
reconstruction + mechanical prothesis	7% (12)	-	6% (12)	-	-
reconstruction + bio- and mechanical prothesis	0.5% (1)	-	0.5% (1)	-	-
type of surgery not specified	**1% (2)**	**-**	**1% (2)**	-	-
Isolated pathogens	68% (121)	65% (22)	68% (143)		
S. aureus	21.5% (38)	11.5% (4)	20% (42)	ns (p>0.1)	ns (p>0.1)
S. viridans	16% (29)	3% (1)	14% (30)	**p<0.02**	ns (p>0.4)
S. epidermidis	4% (7)	17.5% (6)	6% (13)	**p<0.01**	ns (p>0.9)
SOTSV[3]	8.5% (15)	9% (3)	8.5% (18)	ns (p>0.9)	ns (p>0.6)
Enterococci	10% (17)	9% (3)	9.5% (20)	ns (p>0.8)	ns (p>0.9)
Miscellaneous pathogens	5% (9)	9% (3)	6% (12)	ns (p>0.4)	ns (p>0.5)
Mixed infections	3% (6)	6% (2)	4% (8)	ns (p>0.5)	ns (p>0.8)
Culture negative endocarditis	32% (56)	35% (12)	32% (68)	ns (p>0.6	ns (p>0.7)
Infected valves					
one valve / multiple valves	78.5% (139) / 21.5% (38)	94% (32) / 6% (2)	81% (171) / 19% (40)	**p<0.04**	**p<0.02**
aortic valve only	44.5% (79)	70.5% (24)	49% (103)	**p<0.01**	**p>0.4**
mitral valve only	29.5% (52)	20.5% (7)	28% (59)	ns (p>0.2)	ns (p>0.7)
aortic + mitral	20% (35)	6% (2)	17.5% (37)	ns (p=0.052)	**p<0.01**
other valves	6% (10)	3% (1)	5.5% (11)	-	-
Valve damage					
valve stenosis	14% (25)	9% (3)	13% (28)	-	ns (p>0.5)
presence of abscesses	26% (46)	59% (20)	31% (66)	**p<0.01**	ns (p>0.1)
perforation of valvular cusps	79% (140)	29% (10)	71% (150)	-	ns (p>0.5)
valve insufficiency	94% (167)	76.5% (26)	91.5% (193)	-	ns (p>0.6)
valve prolapse	34% (60)	12% (4)	30% (64)	-	ns (p>0.07)
Histological findings					
vegetations	89% (157)	82% (28)	88% (185)	ns (p>0.3)	ns (p>0.2)
vegetation thrombi	58% (102)	41% (14)	55% (116)	ns (p>0.07)	**p<0.03**
calcifications	83% (141)	91% (21)	84% (162)	ns (p>0.2)	ns (p>0.1)
fibrin deposits	44% (74)	48% (10)	44% (84)	ns (p>0.7)	ns (p>0.6)
ulcerations	35% (59)	16% (3)	33% (62)	ns (p>0.09)	ns (p>0.7)
necrosis	33% (56)	21% (4)	32% (60)	ns (p>0.2)	ns (p>0.9)
bacterial colonization	26% (45)	16% (3)	25% (48)	ns (p>0.2)	ns (p>0.4)
lymphocytes	25% (45)	12% (4)	23% (49)	ns (p>0.08)	ns (p>0.06)
granulocytes	63% (111)	32% (11)	58% (122)	**p<0.01**	ns (p>0.5)
Embolic events	36% (64)	21% (7)	34% (71)	ns (p>0.07)	ns (p>0.7)
single embolic event	25% (45)	12% (4)	23% (49)	ns (p>0.08)	ns (p>0.6)
multiple embolic events	9% (16)	9% (3)	9% (19)	ns (p>0.9)	ns (p>0.3)
unknown number of embolic events	2% (3)	-	1.5% (3)	-	-
Sites of emboli[4]					
central nervous system	17% (30)	18% (6)	17% (36)	ns (p>0.9)	ns (p>0.5)
extremities	8% (15)	6% (2)	8% (17)	ns (p>0.5)	ns (p>0.2)
spleen	5% (9)	6% (2)	5% (11)	ns (p>0.8)	ns (p>0.7)
lung	3.5% (6)	-	3% (6)	ns (p>0.1)	ns (p>0.1)
kidney	3% (5)	-	2.5% (5)	ns (p>0.1)	ns (p>0.2)
retina	3% (5)	-	2.5% (5)	ns (p>0.1)	ns (p>0.2)
other sites	5.5% (9)	-	4.5% (9)	ns (p>0.07)	ns (p>0.8)
Mortality					
15-day mortality	8.5% (15)	21% (7)	10% (22)	ns (p=0.052)	-
30-day mortality	11% (20)	29% (10)	14% (30)	**p<0.01**	-
90-day mortality	14% (24)	32% (11)	17% (35)	**p<0.01**	-
median (mean) time to death after surgery (in days; for the 30-day period)	7.5 (10)	5 (8)	7 (9)	-	-
Duration of hospital stay after surgery					
median (mean) time at IMC/ICU[5] (in days)	4 (6)	7 (15)	4 (7)	-	-
median (mean) time at hospital (in days)	12.5 (14)	15 (21)	13 (15)	-	-

Table 1: Study Population

[1] ns = no significance
[2] includes transesophageal and/or transthoracal echocardiography
[3] SOTSV = Streptococci other than *S. viridans*
[4] multiple embolic events seperated into single embolic events
[5] Intermediate Care Unit / Intensive Care Unit

Pathogen	n	%
Staphylococcus aureus	**42**	**20%**
Streptococcus viridans	**30**	**14%**
S. viridans spp.	11	5%
S. mitis	9	4%
S. sanguis	6	3%
S. anginosus ("S. milleri")	4	2%
Enterococci	**20**	**9.5%**
Enterococcus faecalis	12	6%
Enterococcus spp.	6	2.5%
Enterococcus faecium	2	1%
[1]SOTSV	**18**	**8.5%**
S. bovis (group D)	8	4%
S. agalactiae (group B)	3	1%
S. pneumoniae	2	1%
S. haemolyticus (group C)	2	1%
S. beta-haemolyzing	1	0.5%
S. equisimilis	1	0.5%
S. anhaemolyticus	1	0.5%
Staphylococcus epidermidis	**13**	**6%**
Miscellaneous pathogens	**12**	**6%**
Escherichia coli	2	1%
Aerococcus viridans	1	0.5%
Candida albicans	1	0.5%
Enterobacter cloacae	1	0.5%
Gemella morbilorum	1	0.5%
Propionibacterium acne	1	0.5%
Staphylococcus caprae	1	0.5%
Staphylococcus xylosus	1	0.5%
Stenotrophomonas maltophilia (Xanthomonas)	1	0.5%
Staphylococcus spp.	1	0.5%
Gram-positive Coccus	1	0.5%
Mixed infections	**8**	**4%**
Staphylococcus aureus + Enterococcus spp.	2	1%
Enterobacter cloacae + Enterobacter amnigenius	1	0.5%
Enterococcus faecalis + Streptococcus bovis	1	0.5%
Staphylococcus aureus + Enterococcus faecalis	1	0.5%
Streptococcus bovis + Enterococcus spp.	1	0.5%
Streptococcus bovis + Streptococcus equisimilis	1	0.5%
Streptococcus mitis + Staphylococcus aureus	1	0.5%
Culture negative	**68**	**32%**
no detected pathogen	66	31%
history of rheumatic endocarditis	2	1%
TOTAL	**211**	**100%**

[1]SOTSV = Streptococci other than Streptococcus viridans

Table 2: Detected Pathogens

Valve Damage Pattern

	total		NVE		PVE		one valve[3]		av only[4]		mv only[5]		pv/tv only[6]	
Enterococci	**10%**	**(20)**	85%	(17)	15%	(3)	80%	(16)	70%	(14)	10%	(2)	0%	(0)
CNE[1]	**33%**	**(68)**	82%	(56)	18%	(12)	88%	(60)	51.5%	(35)	35.5%	(24)	1.5%	(1)
Misc.pathogens	**6%**	**(12)**	75%	(9)	25%	(3)	58%	(7)	42%	(5)	8%	(1)	8%	(1)
S. aureus	**21%**	**(42)**	90.5%	(38)	9.5%	(4)	88%	(37)	40.5%	(17)	40.5%	(17)	7%	(3)
S. epidermidis	**6%**	**(13)**	54%	(7)	46%	(6)	92%	(12)	61.5%	(8)	23%	(3)	8%	(1)
SOTSV[2]	**9%**	**(18)**	83%	(15)	17%	(3)	67%	(12)	56%	(10)	6%	(1)	6%	(1)
S. viridans	**15%**	**(30)**	97%	(29)	3%	(1)	67%	(20)	37%	(11)	27%	(8)	3%	(1)
TOTAL	**100%**	**(203)**	**84%**	**(171)**	**16%**	**(32)**	**81%**	**(164)**	**49%**	**(100)**	**28%**	**(56)**	**4%**	**(8)**

	av & mv[7]		bilateral IE	
Enterococci	15%	(3)	5%	(1)
CNE[1]	12%	(8)	0%	(0)
Misc.pathogens	42%	(5)	0%	(0)
S. aureus	12%	(5)	0%	(0)
S. epidermidis	8%	(1)	0%	(0)
SOTSV[2]	28%	(5)	6%	(1)
S. viridans	33%	(10)	0%	(0)
TOTAL	**18%**	**(37)**	**1%**	**(2)**

Clinical Findings

	30d-lethality		sepsis		septic focui		embolic events		cerebral emb.		veg. thrombi		vegetations	
Enterococci	15%	(3)	55%	11	45%	9	10%	2	0%	0	55%	11	100%	20
CNE[1]	13%	9	13%	9	6%	4	19%	13	6%	4	31%	21	71%	48
Misc.pathogens	8%	1	17%	2	8%	1	17%	2	8%	1	67%	8	92%	11
S. aureus	21%	9	81%	34	45%	19	64%	27	45%	19	74%	31	98%	41
S. epidermidis	15%	2	46%	6	15%	2	31%	4	15%	2	69%	9	92%	12
SOTSV[2]	11%	2	50%	9	39%	7	67%	12	28%	5	72%	13	94%	17
S. viridans	10%	3	27%	8	20%	1	33%	10	17%	5	60%	18	93%	28
TOTAL	**14%**	**(29)**	**39%**	**79**	**24%**	**48**	**34.5%**	**70**	**18%**	**36**	**55%**	**92**	**87%**	**177**

	abscesses		perforations		insufficiency		stenosis		prolapse	
Enterococci	60%	12	85%	17	100%	20	15%	3	25%	5
CNE[1]	18%	12	54%	37	88%	60	22%	15	34%	23
Misc.pathogens	25%	3	67%	8	83%	10	17%	2	17%	2
S. aureus	33%	14	81%	34	93%	39	5%	2	26%	11
S. epidermidis	46%	6	54%	7	69%	9	0%	0	23%	3
SOTSV[2]	39%	7	78%	14	100%	18	6%	1	22%	4
S. viridans	37%	11	90%	27	100%	30	10%	3	47%	14
TOTAL	**32%**	**65**	**71%**	**144**	**92%**	**186**	**13%**	**26**	**30.5%**	**62**

Histological Findings

	calcification		fibrin deposits		ulcerations		necrosis		slime mold		lymphocytes		granulocytes	
Enterococci	85%	17	61%	11	44%	8	50%	9	32%	6	28%	5	78%	14
CNE[1]	95%	59	32%	20	18%	11	14.5%	9	13%	8	26%	16	45%	28
Misc.pathogens	82%	9	70%	7	44%	4	44%	4	67%	6	33%	3	67%	6
S. aureus	72%	26	46%	17	39%	14	44%	16	30%	11	22%	8	81%	29
S. epidermidis	80%	8	50%	5	40%	4	40%	4	40%	4	20%	2	70%	7
SOTSV[2]	53%	9	65%	11	47%	8	41%	7	29%	5	35%	6	88%	15
S. viridans	93%	28	40%	12	33%	10	30%	9	23%	7	23%	7	57%	17
TOTAL	**84%**	**156**	**45%**	**83**	**32%**	**59**	**32%**	**58**	**35.5%**	**47**	**26%**	**47**	**64%**	**116**

[1] CNE

[2] SOTSV= Streptococci other than Streptococcus viridans

[3] one valve affected only

[4] aortic valve affected only

[5] mitral valve affected only

[6] pulmonary or tricuspid valve affected only

[7] aortic and mitral valve affected

Table 3: Correlated Data

(episodes with two detected pathogens not included; 198 patients; 203 episodes)

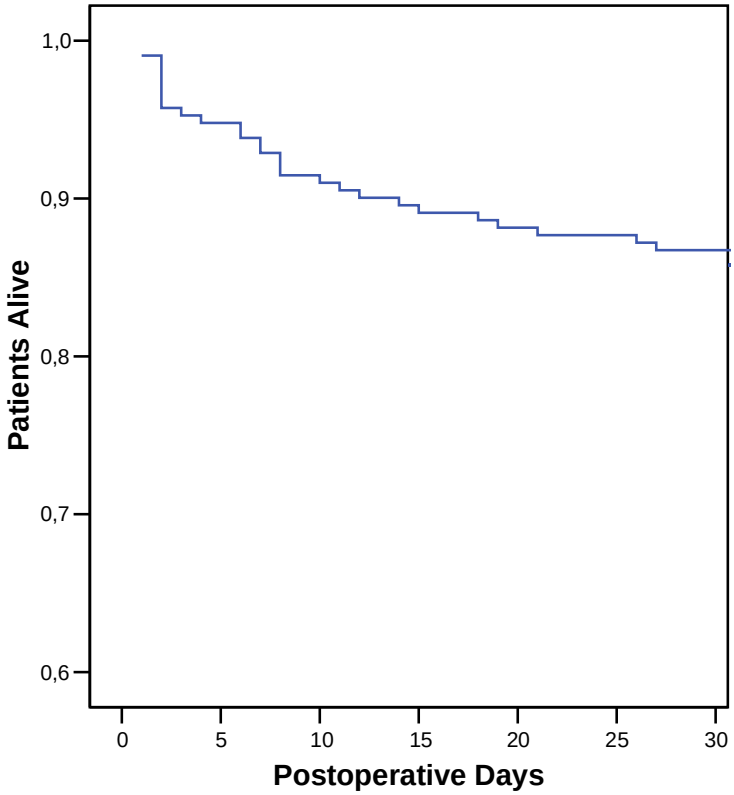

Table IV: Kaplan-Meier Survival Function – 30 days

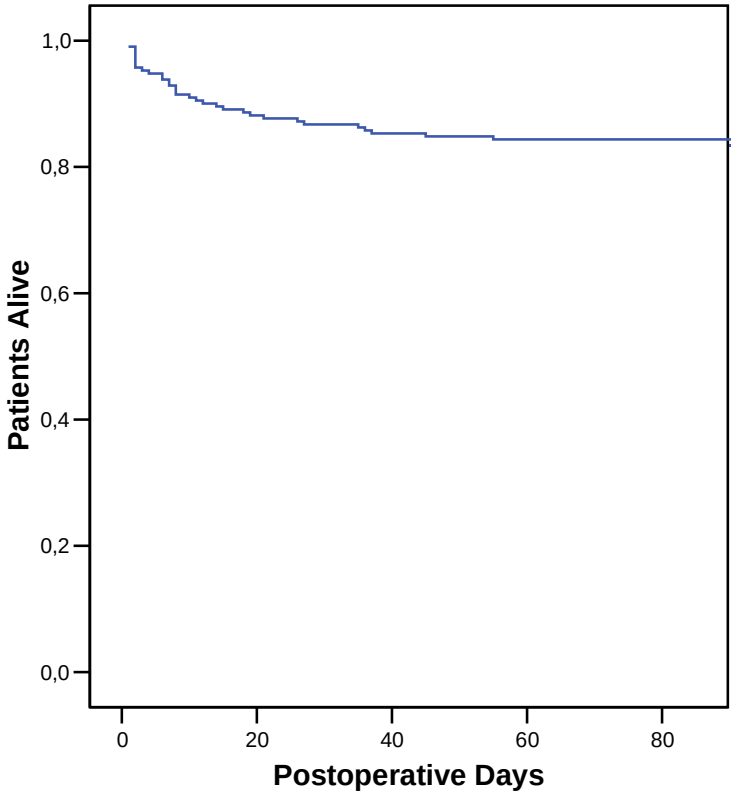

Table V: Kaplan-Meier Survival Function – 90 days

Curriculum Vitae

Zur Person:

Florian Zauner, geboren in Landau an der Isar/Ndb.
15.06.1981
ledig, keine Kinder

Schulausbildung:

Grundschule Landau/Isar	1987-1991
Gymnasium Landau/Isar, Allg. Hochschulreife	
1991-2000	

Zwischenzeit:

Zivildienst im Rettungsdienst Plattling	2000-2001
Prüfung zum Rettungssanitäter	2001

Hochschulausbildung:

Beginn Studium der Humanmedizin an der	2001
Universität Regensburg	
1. Ärztliche Prüfung	2003
Beginn Promotion	2005
6-monatiger Forschungsaufenthalt am UCSD	2006
Medical Center, San Diego, Kalifornien	
Präsentation der Zwischenergebnisse der Doktorarbeit	2007
am European Congress of Clinical Microbiology and	
Infectious Diseases in München	
Praktisches Jahr	2007-2008
in Regensburg (Innere Medizin, Anästhesiologie)	
in Kapstadt (Chirurgie)	
2. Ärztliche Prüfung	2008

Beruflicher Werdegang:

Anstellung als Assistenzarzt	2008
der Abteilung für Anästhesiologie und Intensivmedizin	
an der BG Unfallklinik in Murnau am Staffelsee	