Bacterial Spectrum and Infective Foci in Patients Operated for Infective Endocarditis: Time to Rethink Strategies?

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Abstract

Objective The rising incidence of infective endocarditis (IE) accompanied by the de-escalation of antibiotic prophylaxis and the complexity of surgical treatment makes IE a daunting foe. We reviewed all patients who underwent cardiac surgery for IE at our institution with a focus on causative organisms and infective foci.

Methods A review of 3,952 consecutive patients who underwent cardiac surgery at our institution between January 2013 and December 2017 revealed 160 patients (4%) who were operated for IE.

Results The predominantly affected valves were the aortic (30%) and mitral valve (26.9%) as well as a combination of both (8.8%). A total of 28.8% of patients suffered from prosthetic valve endocarditis (PVE). The most frequently identified causative organisms were *Staphylococcus* (45.7%), *Streptococcus* (27.5%), and *Enterococcus* species (16.7%), which was predominantly associated with PVE ($p = 0.050$). In 13.1% of patients, a causative organism has not been detected. The most frequent infective foci were dental (15%), soft-tissue infections (15%), spondylodiscitis (10%), and infected intravascular implants (8.8%). Relevant predisposing factors were immunosuppression (9.4%) and intravenous drug abuse (4.4%). Septic cerebral infarctions were diagnosed in 28.8% of patients. Postoperative mortality was 22.5%.

Conclusions As the bacterial spectrum and the infective foci are still the "old acquaintances," and with regard to the increasing incidence of IE, current risk–benefit evaluations concerning antibiotic prophylaxis may need to be revisited.

Keywords
- infective endocarditis
- bacterial spectrum
- Infective focus
- antibiotic prophylaxis

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Introduction

Infective endocarditis (IE) is defined as the infection of a native or prosthetic heart valve, the endocardial surface, or an indwelling cardiac device.[1] According to the current guidelines, the use of antibiotic prophylaxis for IE has been restricted because of changes in pathophysiological conceptions.[2–5] On the one hand, the benefit from antibiotic prophylaxis for dental procedures remains unclear and prospective randomized controlled trials are lacking; on the other hand, there is a factual risk of the development of multiresistant organisms and anaphylactic reaction.[3] These observations have been reflected in the guidelines of the American Heart Association (AHA) from 2007, those of the National Institute for Health and Clinical Excellence (NICE) from 2008, and those of the European Society of Cardiology (ESC) from 2009 and 2015.[3,4,6,7] High-risk populations for IE that have been identified include patients after prosthetic valve implantation or after cardiac valve repair using prosthetic material as well as patients after previous IE or untreated cyanotic congenital heart disease.[3] As a result of this de-escalation of antibiotic prophylaxis, a significant decrease of prescription of antibiotic prophylaxis has been observed.[8] At the same time, a significant increase in the incidence of IE was observed especially among high-risk individuals as well as, to a lesser degree, in moderate-risk individuals. An increasing trend in the incidence of IE has also been reported in children.[9] The rising incidence of IE accompanied by the de-escalation of antibiotic prophylaxis after revision of the guidelines in 2007 as well as the complexity of surgical treatment makes IE a daunting foe. It has been reported that the annual incidence of IE is 3 to 10 in 100,000 citizens, with a mortality of up to 30% at 30 days.[10] We reviewed all patients who underwent cardiac surgery for IE at our institution with a focus on causative organisms and infective foci.

Methods

Study Design

Between January 2013 and December 2017, a total of 3,952 patients underwent cardiac surgery at our center; this included 160 patients (4%) who were operated due to IE. Patients with pacemaker infection without indication for heart valve surgery were excluded from the study. Postoperative treatment and data acquisition were performed as part of routine patient care. All procedures described in this study were in accordance with the institutional research committee, national data safety regulations, and the 1964 Helsinki Declaration and its last amendment by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013. Data acquisition was based on our institutional database and has been de-identified. The European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) was used to predict the risk of perioperative mortality.

Definition of Parameters

IE was diagnosed according to the modified Duke criteria and the 2015 ESC guidelines on IE, respectively.[3,11] Early prosthetic valve endocarditis (PVE) was defined as PVE within the first year of surgery.[3] Reoperations were defined as one or more previous major cardiac operation involving opening the pericardium.[12] Cardiogenic shock was defined as persistent mean arterial pressure of less than 65 mm Hg despite inotropic support.[13] Nosocomial pneumonia (NP) was diagnosed according to clinical presentation, elevated leukocyte and C-reactive protein levels, and radiological evidence of pulmonary infiltrates, respectively. Re-exploratative surgery was performed in case of pericardial tamponade or surgical bleeding. Adverse cerebrovascular events were defined as new-onset postoperative neurological symptoms, which were accompanied by a new computed tomography (CT)-confirmed central nervous system lesion.[14]

Microbiological Analysis

Blood Culture Sampling Strategy and Investigation

Blood culture sampling was performed according to the single-sampling strategy,[15] which is favored at our institution. In contrast to the multiple-sampling strategy, which suggests the collection of a pair of blood cultures at different times,[3,16] the single-sampling strategy satisfies both the need to collect the total volume of blood from one single draw filling two to three blood culture sets and the need to decrease contamination rate by limiting the number of punctures.[17] A possible contamination can be identified in that pair of blood cultures that has first been filled. Moreover, antimicrobial treatment is not delayed with this strategy.[15]

Usually, the total volume of blood was collected from one single draw of 40 to 60 mL of blood filling two to three pairs of blood cultures, between 8 and 10 mL of blood in each single bottle. A blood culture pair consists of an aerobic and an anaerobic bottle. Interim storage and transportation to the microbiology laboratory were at room temperature and intended not to exceed 16 hours. Filled blood culture bottles were incubated in the blood culture system BacT/ALERT 3D (bioMérieux, Marcy-l'Etoile, France) for a maximum duration of 5 to 7 days. If the culture system recognized growth in a blood culture bottle, a Gram stain of a blood smear was performed and a drop of the blood culture was plated out on two blood agar plates incubated at 36 ± 1°C aerobically for up to 48 hours and anaerobically for up to 96 hours, respectively, and on a chocolate agar plate incubated microaerophilically for up to 48 hours. Species identification was performed with MALDI Biotyper (Bruker Daltonics GmbH, Bremen, Germany).

Bacterial DNA Detection from Native Valve Tissue and Valve Abscess Material

Valve tissue was incubated in a buffer ATL (Qiagen, Venlo, the Netherlands) together with proteinase K at 56°C overnight followed by genomic DNA purification using the QIAamp DNA Mini Kit (Qiagen, Venlo, the Netherlands) according to the manufacturer's instructions. Detection of bacterial or fungal DNA was performed by polymerase chain reaction (PCR) with broad-range primers for the amplification of 16S rRNA or 18S rRNA, respectively.[18,19] PCR products are detected by agarose

gel electrophoresis and are subsequently sequenced applying the primers used for PCR.

Culture of Native Valve Tissue and Prosthetic Valve

Excised valve tissue or prosthesis is transported in a 70-mL sterile container immediately to the microbiology laboratory. The specimen is incubated in thioglycolate broth for up to 14 days. Macroscopic inspection is performed daily on days 1 to 4, and on days 7 and 14, respectively. If growth is suspected or visible, e.g., gas production or turbidity of thioglycolate broth, or the specimen has been incubated for 14 days, then broth is taken by a 10-µL loop and plated out on two blood agar plates, incubated at 36 ± 1°C aerobically for up to 48 hours and anaerobically for up to 96 hours, respectively, and on a chocolate agar plate, incubated microaerophilically for up to 48 hours. Species identification was performed with MALDI Biotyper (Bruker Daltonik GmbH, Bremen, Germany).

Statistical Analysis

Data were analyzed using the IBM SPSS Statistics Data Editor version 20. They were tested for normal distribution using the Shapiro–Wilk test as well as the Kolmogorov–Smirnov test with Lilliefors correction. Categorical variables were evaluated using Fisher's exact test and continuous variables were evaluated using the Mann–Whitney *U* test. The null hypothesis was rejected and significant difference was assumed with p-values ≤ 0.05. Results are presented as medians with interquartile ranges and percentages, respectively.

Additionally, we reviewed the nationwide database of the German Federal Statistical Office (Statistisches Bundesamt, Destatis) for the number of patients being diagnosed with acute and subacute IE (International Classification of Diseases-10 [ICD-10] code I33.0).

Results

Baseline Parameters and Details of Surgery

Patient characteristics and baseline parameters are outlined in ►**Table 1**. Median age was 66 years (57–74), with 30.6% of the patients being female. The median EuroSCORE II was 14.5% (5.7–39.9%). Median left ventricular ejection fraction was 45% (40–55%). At the time of surgery, 19 patients (11.9%) presented with a left ventricular ejection fraction of less than 30%. Most frequently diagnosed relevant comorbidities were chronic kidney disease in 38.8% of the investigated patients, chronic obstructive pulmonary disease in 37.5%, and pulmonary hypertension in 33.1%. In 28.8% of patients, preoperative septic cerebral infarctions have been diagnosed.

The predominantly affected valve was the aortic valve (30%), followed by the mitral valve (26.9%). Triple-valve endocarditis occurred in 1.3% of patients. A minority of patients presented with right-sided IE, namely, tricuspid and pulmonary valve endocarditis, which was diagnosed in two patients, respectively. A total of 28.8% of surgical procedures were reoperations for PVE, with a median interval between the first and second operation of 5.2 years (1.7–11.1). Early PVE was diagnosed in nine patients (5.6%). The causative organisms for early PVE were mainly gram-positive bacteria (*Enterococcus faecalis*, $n = 3$; *Staphylococcus aureus*, $n = 4$; and *Staphylococcus epidermidis*, $n = 2$). A total of 53.1% of patients underwent urgent or emergency operation. Concerning the surgical technique, valve repair was performed in 4 patients (2.5%), whereas mechanical prostheses were implanted in 47 patients (29.4%). Aortic root repair was performed in 11 patients (6.9%), whereas aortic root replacement was necessary in 17 patients (10.6%), with homografts being implanted in 13 patients (8.1%).

Duke Criteria

The evaluation of the Duke criteria (►**Table 2**) revealed a total of 115 patients (71.8%) presenting with two major criteria and a total of 21 patients (13.1%) presenting with one major criterion and three minor criteria, whereas 24 patients (15%) did not meet the Duke criteria. A positive blood culture was available in 121 patients (75.6%). Echocardiographic evidence of vegetations was present in 148 patients (93%), whereas echocardiographic findings were consistent with respect to IE in 11 patients (6.9%).

Postoperative Outcome

A total of 124 patients (77.5%) survived to discharge. Postoperative outcome of survivors and nonsurvivors is summarized in ►**Table 3**. The most frequently observed adverse events were cardiogenic shock in 67 patients (41.9%), acute kidney injury in 64 patients (40%), and NP in 61 patients (38.1%) (definitions are provided earlier). All of them occurred significantly more often in the nonsurvivor group. Extracorporeal life support (ECLS) was required in a total of seven patients (4.4%), whereas an intra-aortic balloon pump was applied in five patients (3.1%). Median time on ECLS was 6 days (1–8). Time on mechanical ventilation was 26 hours (9–119), with a median stay on intensive care unit of 5 days (2–12).

Bacterial Spectrum

No causative organisms were detected in 13.8% of the cases. Microbiological results are presented in ►**Table 4**. The most frequent causative organisms were *Staphylococcus* species (spp.), which accounted for 45.7% of the infections detected, followed by *Streptococcus* spp. (27.5%) and *Enterococcus* spp. (16.7%). Gram-negative bacteria have been identified in 3.7% of patients. Fungal infection occurred in one patient. *Staphylococcus* spp. can be further subdivided into methicillin-sensitive *S. aureus* (MSSA) (27.6%), methicillin-resistant *S. aureus* (3.6%), and others (14.5%). *Streptococcus* spp. were predominantly identified as viridans group streptococci (20.3%) followed by streptococci group B and C (5.8%). *Streptococcus* spp. were strongly associated with mitral valve endocarditis ($p = 0.035$), whereas *Enterococcus* spp. were found to be associated with PVE ($p = 0.050$) (►**Table 5**).

Infective Foci

Infective foci and predisposing factors are outlined in ►**Table 6**. The most frequently identified infective foci were dental (15%), soft tissue infections (15%),

Table 1 Demographic parameters and details of surgery

	Total ($n = 160$)
Demographic parameters	
Age (y)	66 (57–74)
Female gender (%)	49 (30.6)
EuroSCORE II (%)	14.5 (5.7–39.9)
NYHA class	3 (3–3)
Echocardiographic data	
Affected valves	
Isolated aortic valve (%)	48 (30)
Isolated mitral valve (%)	43 (26.9)
Isolated tricuspid valve (%)	2 (1.3)
Isolated pulmonary valve (%)	2 (1.3)
Aortic and mitral valve (%)	14 (8.8)
Mitral and tricuspid valve (%)	3 (1.9)
Aortic mitral and tricuspid valve (%)	2 (1.3)
Prosthetic valve endocarditis (%)	46 (28.8)
LVEF (%)	45 (40–55)
Moderate to severe aortic regurgitation (%)	83 (51.9)
Moderate to severe mitral regurgitation (%)	72 (45)
Moderate to severe tricuspid regurgitation (%)	8 (5)
Pulmonary hypertension (%)	53 (33.1)
Comorbidities	
Arterial hypertension (%)	137 (85.6)
Atrial fibrillation (%)	77 (48.1)
Insulin-dependent diabetes (%)	54 (33.8)
Chronic kidney disease (%)	62 (38.8)
Hyperlipidemia (%)	86 (53.8)
Hyperuricemia (%)	15 (9.4)
Chronic obstructive pulmonary disease (%)	60 (37.5)
Coronary artery disease (%)	49 (30.6)
Peripheral artery disease (%)	38 (23.8)
Preoperative septic cerebral infarction (%)	46 (28.8)
Details of surgery	
Median interval between first and second operation (y)	5.2 (1.7–11.1)
Overall reoperations (%)	50 (31.3)
Urgency	
Elective surgery (%)	73 (45.6)
Urgent surgery (%)	49 (30.6)
Emergency surgery (%)	36 (22.5)
Salvage (%)	2 (1.3)
Surgical technique	
Valve repair (%)	4 (2.5)
Mechanical prosthesis (%)	47 (29.4)
Biological prosthesis (%)	92 (57.5)

(*Continued*)

Table 1 (*Continued*)

	Total ($n = 160$)
Homograft (%)	17 (10.6)
Aortic root repair (%)	11 (6.9)
Aortic root replacement (%)	15 (9.4)
Atrial patch repair (%)	4 (2.5)

Abbreviations: EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
Note: Data are presented as median (25th–75th percentiles) or absolute numbers (percentages).

Table 2 Duke Criteria for Infective Endocarditis

	Overall ($n = 160$)
Major criteria	
Positive blood culture for typical infective endocarditis organisms	121 (75.6)
Echocardiogram with oscillating intracardiac mass on valve or supporting structures	148 (92.5)
Minor criteria	
Predisposing heart condition or intravenous drug abuse	37 (23.1)
Temperature $> 38°C$	150 (93.8)
Vascular phenomena	73 (45.6)
Immunologic phenomena	10 (6.3)
Microbiological evidence	10 (6.3)
Echocardiographic findings consistent with endocarditis	11 (6.9)
Diagnosis	
Patients with two major criteria	115 (71.8)
Patients with one major criterion and three minor criteria	21 (13.1)
Patients with five minor criteria	0 (0)
Patients not meeting the Duke criteria	24 (15)

Note: Data are presented as absolute numbers (percentages).

spondylodiscitis (10%), and infected intravascular implants (8.8%). Relevant predisposing factors were immunosuppression (9.4%) and intravenous drug abuse (4.4%). Preceding interventional or surgical procedures, namely, abdominal/general surgery procedures as well as ear-nose-throat (ENT) interventions and neurosurgical interventions, accounted for 10.7% of infections. In our cohort, the infective focus remained unknown in 17.5% of patients.

Discussion

Our current review of the Destatis database, depicted in ►**Fig. 1**, confirmed the increasing number of patients being diagnosed with acute and subacute IE (ICD code I33.0). In German hospitals, a total of 7,104 patients were hospitalized due to IE in 2015; this rose to 7,586 patients in 2016 and 8,017 patients in 2017. A former analysis by Keller et al[20] revealed a total of 94,364 patients with the diagnosis of IE between January 2005 and December 2014, with a mean prevalence of 11.6 per 100,000 citizens per year during this period. This trend has also been observed internationally: in the United Kingdom, a significant increase of IE has been reported,[3] as well as in the United States.[8] Whether the restriction of antibiotic prophylaxis is associated with the increasing prevalence of IE remains unclear.[3,21] As microbiological data were not provided in the majority of available databases, reliable conclusions on infective foci and the adequacy of antibiotic prophylaxis cannot be drawn.[3,8] So far, there are only few data available focusing on the characterization of patients referred to cardiac surgery. The most recent prospective cohort study is the EURO-ENDO registry, including 3,116 patients from 40 countries (including 132 patients from German centers); among them, 1,596 patients underwent cardiac surgery.[22] As Baumgartner emphasizes in his commentary on the recent ESC guidelines, there were no reliable data available supporting the former recommendations or supporting the revised version. Accordingly, the revised version was not based on new research results but rather on a new interpretation of available data.[21] As a consequence, the authors of the ESC guidelines emphasized the importance of a close observation of the further development of the incidence of IE.[3,21]

Table 3 Postoperative Outcomes

	Survivors ($n = 124$)	Nonsurvivors ($n = 36$)	Overall ($n = 160$)	p
Adverse events				
Adverse cerebrovascular events	4 (3.2)	6 (16.7)	10 (6.3)	0.003
Re-explorative surgery	12 (9.7)	8 (22.2)	20 (12.5)	0.046
Pacemaker implantation	15 (12.1)	1 (2.8)	16 (10)	0.102
Surgical site infection	8 (6.5)	1 (2.8)	9 (5.6)	0.401
Cardiogenic shock	37 (29.8)	30 (83.3)	67 (41.9)	<0.001
Tracheostomy	9 (7.3)	5 (13.9)	14 (8.8)	0.217
Renal replacement therapy	36 (29)	28 (77.8)	64 (40)	<0.001
Nosocomial pneumonia	41 (33.1)	20 (55.6)	61 (38.1)	0.015
HIT type II	2 (1.6)	0 (0)	2 (1.3)	0.445
Acute respiratory failure	10 (8.1)	17 (47.2)	27 (16.9)	<0.001
Right ventricular failure	11 (8.9)	17 (47.2)	28 (17.5)	<0.001
Outcome on ICU				
ECLS	3 (2.4)	4 (11.1)	7 (4.4)	0.025
Time on ECLS (d)	6 (6–6)	4 (1–9)	6 (1–8)	0.857
IABP support	1 (0.8)	4 (11.1)	5 (3.1)	0.002
PMV time (h)	21 (10–77)	67 (10–272)	26 (9–119)	0.072
Length of ICU stay (d)	5 (2–11)	6 (2–20)	5 (2–12)	0.523

Abbreviations: ECLS, extracorporeal life support; HIT, heparin-induced thrombocytopenia; IABP, intra-aortic balloon pump; ICU, intensive care unit; PMV, postoperative mechanical ventilation.
Data are presented as median (25th–75th percentiles) or absolute numbers (percentages).

Bacterial Spectrum and Infective Foci

The current guidelines report that there is no compelling evidence that indicates that respiratory tract, gastrointestinal, genitourinary, dermatological, or musculoskeletal procedures may cause bacteremia and, thereby, put patients at risk for IE.[3] Currently, prophylaxis is only recommended in the context of infection. However, our data suggest that soft-tissue infections, bacteremic pneumonia, and urinary tract infection account for a total of 22.5% of infective foci. Although preceding interventional or surgical procedures have not been documented in all of these patients, our data imply that these body regions seem to be relevant potential portals of entry. Therefore, an antibiotic prophylaxis only in case of clinically apparent infection is at least associated with a potentially increased risk of bacterial spread.

In the investigated study population, a dental focus has been reported in 15% of patients, whereas in the EURO-ENDO registry the portal of entry was dental in 9.8%. Accordingly, viridans group streptococci have been identified in 17.4% of patients in our study population, compared with 12.4% in the registry.[22] Our results, thus, contradict one of the main messages from the analyses of the EURO-ENDO registry—that endocarditis caused by oral viridans group streptococci was less frequent compared with previous studies (Euro-Heart Survey [13%] and the International Collaboration on Endocarditis-Prospective Cohort Study [17%]).[23,24] As the EURO-ENDO registry includes only 132 patients (4.2%) from German centers, there may be regional differences concerning the underlying bacterial spectrum asking for locally adapted preventive strategies.[22] As highly effective antibiotics against streptococci are available, which are associated with a very low rate of serious side effects, the question remains whether the restriction of the target population to the highest-risk group is justified.[3,21]

Other frequent causative organisms identified in our study population were MSSA (27.6%) and *E. faecalis* (16%), which have been found in a similar proportion in the EURO-ENDO registry.[22] Earlier studies reported a significantly lower incidence of *Enterococcus* spp. (8–10%), which indicates a relevant increase of this causative organism.[24,25] As *Enterococcus* spp. were strongly associated with prosthetic valve IE not only in the investigated patient population but also in previous studies,[22,26] a modification of antibiotic prophylaxis may be indicated in this high-risk patient group. As mentioned earlier, the restriction of antibiotic prophylaxis in the context of interventional or surgical gastrointestinal procedures to infection might be too narrow. With regard to the affected valves, in our study group prosthetic valves accounted for approximately 30% of infections and were, thus, equally affected compared with native aortic and mitral valves. As PVE is associated with a substantially elevated perioperative risk compared with native valve IE[26] and taking into account the increasing incidence of enterococcus species, as described earlier, it should be one focus of future modifications of current preventive strategies.

Table 4 Bacterial spectrum

Detected pathogens	Overall ($n = 138$)
Gram-positive bacteria	
Staphylococcus spp.	
MSSA[a]	38 (27.6)
MRSA	5 (3.6)
Staphylococcus lugdunensis[b]	7 (5.1)
Other CoNS[c]	13 (9.4)
Enterococcus species	
Enterococcus faecalis	22 (16)
Enterococcus faecium	1 (0.7)
Streptococcus species	
Streptococcus group B	
Streptococcus agalactiae	5 (3.6)
Streptococcus group C	
Streptococcus dysgalactiae	2 (1.5)
Streptococcus equi	1 (0.7)
Streptococcus pneumoniae	2 (1.5)
Viridans group streptococci orally occurring[d, e]	24 (17.4)
Viridans group streptococci not orally occurring[f]	4 (2.9)
Other gram-positive bacteria	
Cutibacterium acnes	4 (2.9)
Gemella haemolysans	1 (0.7)
Gemella morbillorum	1 (0.7)
Lactococcus garvieae	1 (0.7)
Tropheryma whipplei	1 (0.7)
Aerococcus urinae	1 (0.7)
Gram-negative bacteria	
Escherichia coli	1 (0.7)
Morganella morganii	1 (0.7)
Klebsiella pneumoniae	1 (0.7)
Neisseria mucosa	1 (0.7)
Salmonella Choleraesuis var. Kunzendorf	1 (0.7)
Mold fungus	
Aspergillus fumigatus	1 (0.7)

Abbreviations: CoNS, coagulase-negative staphylococci; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *S. aureus*.
[a]Includes two double infections: MSSA + *S. lugdunensis* ($n = 1$ and MSSA + *Streptococcus mitis*/*oralis* ($n = 1$).
[b]Includes one double infection: MSSA + *S. lugdunensis* ($n = 1$)
[c]Detected CoNS: *Staphylococcus epidermidis* ($n = 12$), *Staphylococcus warneri* ($n = 1$).
[d]Includes one double infection: MSSA + *S. mitis*/*oralis* ($n = 1$).
[e]Viridans group streptococci, orally occurring:
Streptococcus anginosus group: *S. anginosus* ($n = 1$); *S. mitis* group: *S. oralis* ($n = 2$), *S. mitis* ($n = 4$), *S. mitis*/*oralis* ($n = 7$), *Streptococcus cristatus* ($n = 2$); *Streptococcus mutans* group: *S. mutans* ($n = 2$); *Streptococcus salivarius* group: *S. salivarius* ($n = 3$); *Streptococcus sanguinis* group: *S. sanguinis* ($n = 3$).
[f]Viridans group streptococci, not orally occurring:
Streptococcus gallolyticus group: *S. gallolyticus* ($n = 4$).
Note: Data are presented as absolute numbers (percentages).

Table 5 Details of valves affected with reference to causative organisms

	Overall ($n = 138$)	p[a]
Mitral valve		
Staphylococcus spp.	26 (18.8)	0.616
Streptococcus spp.	20 (14.5)	0.035
Enterococcus spp.	6 (4.3)	0.173
Others	4 (2.9)	0.784
Aortic valve		
Staphylococcus spp.	20 (14.5)	0.243
Streptococcus spp.	17 (12.3)	0.446
Enterococcus spp.	8 (5.8)	0.505
Others	8 (5.8)	1
Prosthetic valve		
Staphylococcus spp.	22 (16)	1
Streptococcus spp.	6 (4.3)	0.151
Enterococcus spp.	11 (8)	0.050
Others	3 (2.2)	1.000

[a]Fisher's exact test.
Note: Data are presented as absolute numbers (percentages).

Table 6 Infective foci and predisposing factors

	Overall ($n = 160$)
Infective foci	
Dental focus	24 (15)
Soft tissue infection	24 (15)
Spondylodiscitis	16 (10)
Intravascular implant infection	14 (8.8)
Abdominal/general surgery	13 (8.1)
Bacteremic pneumonia	7 (4.4)
Urinary tract infection	5 (3.1)
Extravascular implant infection	4 (2.5)
Ear, nose, and throat intervention	2 (1.3)
No focus identified	28 (17.5)
Predisposing factors	
Immunosuppression	15 (9.4)
Intravenous drug abuse	7 (4.4)

Note: Data are presented as absolute numbers (percentages).

Diagnosis of IE

For the diagnosis of IE, the Duke criteria have been reported to be the gold standard.[11] They have undergone several adjustments over the years including the St. Thomas modifications.[27] However, its diagnostic value is limited. In our cohort, a total of 15% of patients did not meet the Duke criteria. Endocarditis has been reported to be classified as definite in 21% of patients as per the original Duke criteria, while 32% were diagnosed as definite by the modified Duke

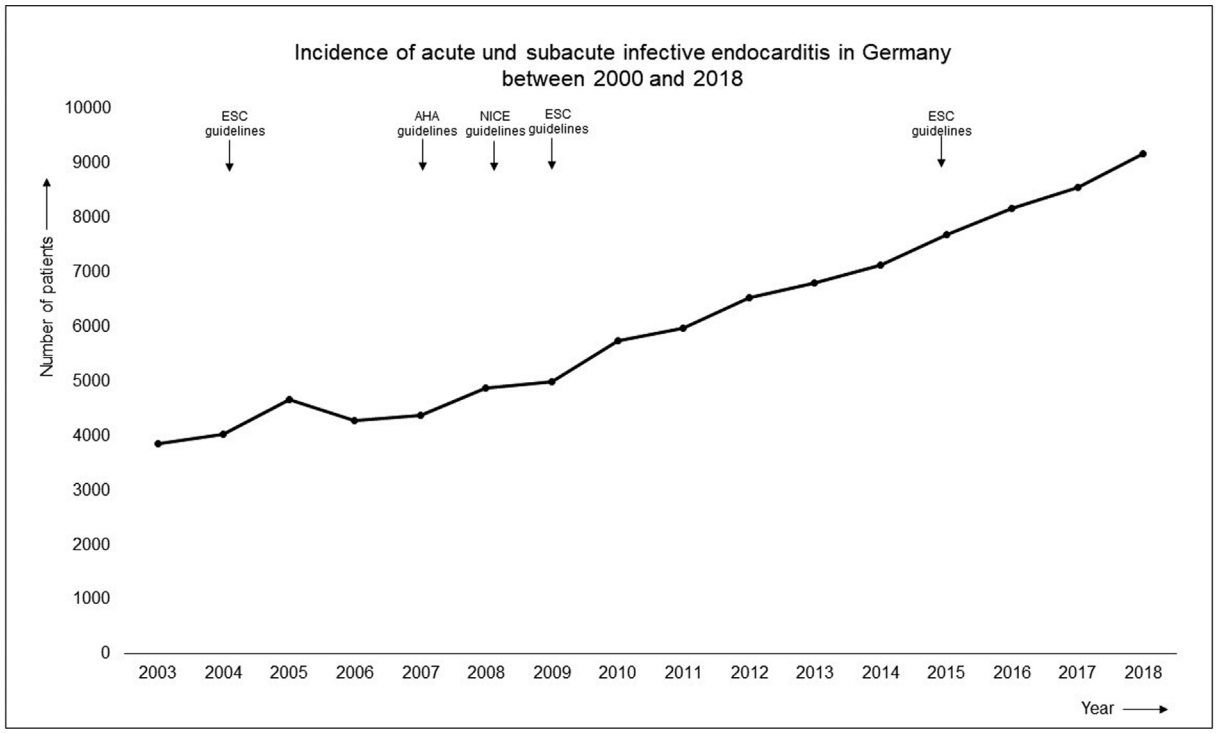

Fig. 1 Incidence of acute and subacute infective endocarditis and heart valve procedures in Germany between 2003 and 2018. (Data sourced from German Federal Statistical Office [Statistisches Bundesamt, Destatis].) AHA, American Heart Association; ESC, European Society of Cardiology; NICE, National Institute for Health and Clinical Excellence.

criteria compared with 62% applying the St Thomas modifications.[28] These data imply a significant underreporting of IE. Therefore, further adjustment of these criteria has been suggested.[28,29] Even in patients who do not develop fulminant endocarditis, a subclinical endocarditis may lead to calcification of heart valves, which, in turn, in the long run could lead to the development of structural heart valve disease or late IE. Patients with structural heart valve disease have been shown to test positive for bacterial DNA, with around 30% of patients showing signs of a polymicrobial infection.[30,31]

Having those silent infections in mind with its potentially harmful consequences for the patient in addition to the increasing numbers of clinically obvious IE (►**Fig. 1**), the question arises whether the risk–benefit evaluation concerning a prophylactic antibiotic therapy has to be revised.

Survival and Adverse Events

In-hospital mortality was 22.5% in the study group compared with 17.1% mortality reported in the EURO-ENDO registry, where a mixed surgical and nonsurgical patient population has been included.[22] In patients suffering from IE, adverse cerebrovascular events are one of the most feared complications as it may be associated with devastating consequences. In our cohort, the proportion of patients who were diagnosed with preoperative septic cerebral infarctions was as high as 28.8%. In addition, a total of 6.3% suffered from postoperative adverse cerebrovascular events. These numbers reflect the severity of the disease particularly in those patients referred to cardiac surgery. Pizzi et al[29] reported that septic cerebral events may assume several clinical identities such as ischemic and hemorrhagic stroke, infective intracranial aneurysm, and meningitis. They identified certain causative organisms to be more likely to cause cerebral embolism, such as *S. aureus*, *Candida* spp., and gram-negative bacteria from the HACEK group (*Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* spp.).[29] These findings were similar to those reported earlier and offer a potential target for a more goal-directed antibiotic prophylaxis.

In sum, as Baumgartner emphasized, due to the insufficient database not only for the previously recommended, rather wide-ranging prophylactic antibiotic strategy but also for the currently recommended restriction, individual decisions are required, up to the maintenance of the former recommendations.[21] Therefore, and based on the increasing number of patients presenting with severe courses of IE in our cardiac surgery departments associated with poor postoperative outcomes, our institutional protocol has already been modified toward an expansion of the indications concerning postoperative antibiotic prophylaxis.

Limitations

The retrospective single-center design and the limited number of patients are associated with a reduced power of statistical analyses.

Conclusions

IE remains a life-threatening disease associated with substantial morbidity and mortality in cardiac surgery patients.

As the predominant infective foci as well as the most frequent pathogens are still the "old acquaintances" for which standardized effective and low-risk protocols for antibiotic prophylaxis are available and with regard to the continuously increasing incidence of IE, current risk–benefit evaluations may need to be revisited.

Authors' Contributions

Shekhar Saha Data curation, formal analysis, visualization, writing – original draft and revisions
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Conflict of Interest

The authors of this manuscript declare that they have no conflicts of interest, had full control of the design and methods of the study, data analysis, and production of the written report, and that no funding supported this study.

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