Clinical manifestations of infective endocarditis in relation to infectious agents: An 8-year retrospective study

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Aim. To compare clinical complications and outcomes of infective endocarditis (IE) episodes caused by *Staphylococcus aureus* (*S. aureus*) and other most frequent aetiological agents (streptococci, enterococci, coagulase-negative staphylococci, and culture-negative IE).
Methods. A total of 117 IE episodes assessed by all internal medicine services of a major teaching institution in the Czech Republic over an eight-year period were identified.
Results. We found that *S. aureus* IE episodes (n = 36) were significantly more associated with systemic embolism (41.7% vs 18.5%, $P = 0.01$), severe sepsis/septic shock (33.3% vs 3.7%, $P < 0.0001$), and in-hospital mortality (33% vs 12.3%, $P = 0.01$). No differences in local, structural, and/or functional complications (cardiac abscess formation, impaired integrity of the valvular apparatus, conduction disturbances, or incidence of heart failure) were observed between studied groups. Long-term survival estimates were significantly improved in patients with IE caused by agents other than S. aureus (13.78 median years vs 5.48 median years, $P=0.03$).
Conclusions. IE episodes caused by *S. aureus* are associated with both increased short-term and long-term mortality. Of all the studied parameters, only systemic embolism and severe sepsis/septic shock predicted in-hospital mortality.

Key words: infective endocarditis, *Staphylococcus aureus*, systemic embolism, complications of infective endocarditis, septic shock, mortality

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INTRODUCTION

Despite the latest advances in both medical and surgical therapies, the syndrome of infective endocarditis (IE) continues to be characterised by serious complications and remains a life-threatening infection.

Based on both institutional and multinational studies it is now widely accepted that clinical manifestations, and the impact on clinical outcomes, of IE vary in relationship to the following factors: causative agents, localisation of infection and comorbidities[1-6]. Geographical location also plays an important role given the prevalence of rheumatic carditis, i.v. drug use and the abundance of implanted artificial materials.

In recent decades, Staphylococcus aureus (S. aureus) has become the most important aetiological agent of IE – resulting in the worst outcomes, the highest rates of complications and highest mortality[7-10]. In-hospital mortality has been reported at between 30% and 71% (ref.[11-13]). However, it remains uncertain whether its devastating effects are based more on local destruction than on other systemic impacts and complications.

Aim of the study

The aim of the study was to compare clinical manifestations and clinical outcomes of *S. aureus* IE and IE caused by most frequent aetiological agents (streptococci, enterococci, coagulase-negative staphylococci and culture-negative IE). In addition, we attempted to determine the factors responsible for supposed poor outcomes of IE caused by *S. aureus*. Finally, we aimed to determine long-term mortality of IE episodes depending on causative agents.

MATERIALS AND METHODS

We conducted a retrospective survey of adult IE patients, admitted over an eight-year period between November 1998 and November 2006 to the Department of Internal Medicine at University Hospital Hradec Kralove, Charles University, Czech Republic (the main referral centrein Eastern Bohemia). All included cases met the modified and definite Duke criteria[14].

Personal data, physical examination findings and results of electrocardiogram, echocardiographic, radiographic and microbiological examinations were evaluated along with clinical courses, patient outcomes, complications, indications for surgery and surgical findings.

To assess long-term mortality as a result of IE episodes, up-to-date survival estimates for each patient were evaluated by either a direct telephone call to the patient and/or a follow-up at our institution, or from indirect information on survival of the patient as provided by either

the patient's general practitioner/cardiologist or insurance company. All patients who survived the active phase of IE were included in a long-term follow up. Due to the retrospective nature of the origin of research, determination of cause of death was not included in the follow-up assessment.

From the descriptive statistics available, absolute and relative frequencies were used. In order to test the relationship between two discrete variables, we used the χ^2-test. Where expected frequencies were less than 5, we used Fisher's exact test. To search for independent predictors of mortality, we used logistic regression, the results of which are presented as OR (odds ratio) and 95% confidence intervals for OR. To confirm the correlation between discrete and continuous variables, we used the biserial correlation coefficient. The Kaplan-Meier method was used to estimate long-term survival and the Cox regression model was used to determine long-term mortality risk factors.

Definitions

Local structural complications involved perforation or prolapse of the valve leaflet and intracardiac abscess. For the purposes of the study, only the following cases were considered: newly formed prolapses, prolapses of atypical localisation, prolapses with thinning in the prolapse area and apparent failure of chordae integrity.

The maximum dimension of vegetation was considered. In the presence of multiple vegetations, the largest was selected. The mobility of vegetation was assessed by the physician performing the examination and evaluated using a simplified 2-point scale: 1 – absent (fixed vegetation with no detectable independent motion), 2 – present (presence of a mobile free edge that either remains within the same chamber throughout the cardiac cycle or crosses the coaptation plane of the leaflets during the cardiac cycle).

Conduction impairment was diagnosed where a new 1st-3rd AV block associated with an IE episode was reported.

Congestive heart failure was diagnosed on the basis of clinical assessments conducted by the team of attending physicians. Only new episodes showing conclusive IE-associated progression of heart failure were included.

Clinically significant embolism of vegetation was considered for the purposes of the study. Janeway lesions and splinter haemorrhages were not included. All patients underwent abdominal ultrasound during the course of the IE episode. A CT/MRI scan was indicated in cases where there was a clinical suspicion of an embolic episode.

Severe sepsis was defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion. Septic shock was defined as the presence of acute circulatory failure during sepsis, characterised by persistent arterial hypotension despite adequate volume resuscitation.

Culture-negative endocarditis was defined as endocarditis without aetiology following inoculation of at least three independent blood samples in a standard blood-culture system with negative cultures after seven days of incubation and subculturing. Systematic serological testing was not part of the study.

Relapsing IE was defined as an episode of IE provided it occurred within six months of completing medical therapy for a prior episode of IE, and that the same pathogen was identified in the relapsing and earlier episodes.

Recurrent IE was defined as an episode provided it occurred more than six months after the completion of medical therapy, or less than six months only where the pathogen that caused the recurrent bout differed from the one which caused the earlier attack.

Complete follow-up (long-term mortality) was defined as the availability of information up until either the end of the study (1st March 2015) or death.

RESULTS

A total of 117 IE episodes among 106 patients were identified (85 males, 21 females; mean age 57 ± 14.8 years; median age 59.6 years; range: 20 to 79 years). There were six relapses and five recurrences (seven patients had two

Table 1. Demographic data of IE episodes caused by *S. aureus* and other agents leading to IE episodes.

	S. aureus	Other agents leading to IE episodes	*P*
Number of patients/episodes of IE	32/36	74/81	–
Age (median, years)	64.1	58.1	0.15
Males/females	25/7	60/14	0.73
Aortic valve native/prosthesis	14 (38.9%) / 4 (11.1%)	34 (42%) / 15 (18.5%)	0.84
			0.34
Mitral valve native/prosthesis	19 (52.8%) / 0	29 (35.8%) / 2 (2.5%)	0.06
			1.00
Tricuspid valve native/prosthesis	1 (2.8%) / 0	4 (4.9%) / 0	1.00
Implantable device/other	3 (8.3%) / 0	4 (4.9%) / 1 (1.2%)	0.43
			1.00
Cardiac surgery/ extraction of implantable device	10 (30.3%) / 3 (100%)	26 (33.8%) / 4 (100%)	0.70
			1.00

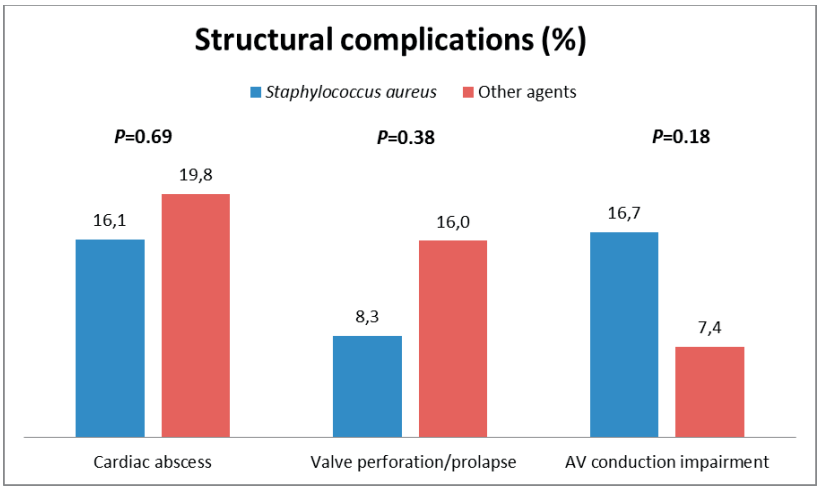

Fig. 1. Structural complications.

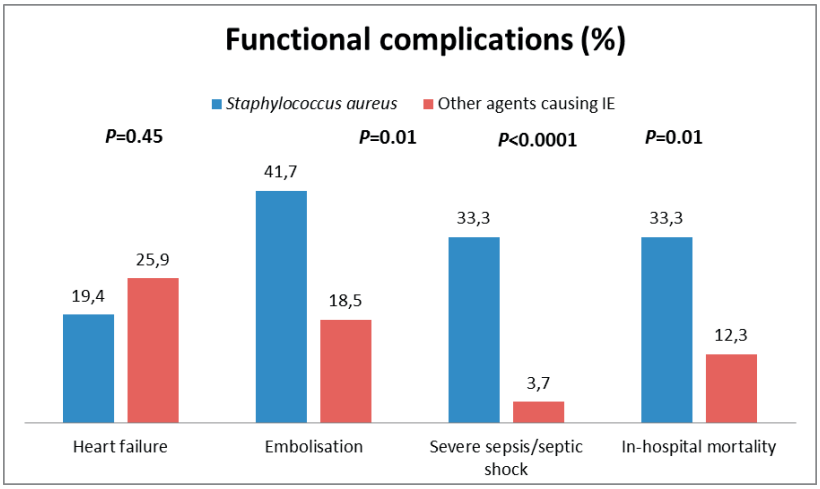

Fig. 2. Functional complications.

Table 2. Incidence of embolic episodes.

	Brain	Kidney	Spleen	Liver	Extremities	Coronary arteries	Spine
S. aureus (n=36)	11/36 (30.6%)	4/36 (11.1%)	4/36 (11.1%)	1/36 (2.8%)	1/36 (2.8%)	1/36 (2.8%)	1/36 (2.8%)
Other agents leading to IE episodes (n=81)	8/81 (9.9%)	2/81 (2.5%)	2/81 (2.5%)	0/81 (0%)	2/81 (2.5%)	5/81 (6.2%)	0/81 (0%)
P	0.01	0.07	0.07	0.31	1.00	0.67	0.31

episodes, and two patients had three episodes). There was no difference in mean age based on gender (male versus female, 57.4 years versus 57.2 years).

Thirty-six IE episodes caused by *S. aureus* were identified (30.8%, Group 1). The remaining 81 IE cases (Group 2) were caused by coagulase-negative staphylococci (17 episodes, 14.5%), streptococci (16 episodes, 13.7%), enterococci (15 episodes, 12.8%), polymicrobial IE (5 episodes, 4.3%), gram-negative IE (5 episodes, 4.3%), Propionibacterium species (1 episode, 0.9%) and Lactococcuslactis (1 episode, 0.9%). In 21 episodes (17.9%) the causal agent was not identified (culture-

Table 3. Relationship between vegetation mobility and systemic embolism.

	IE episodes with systemic embolism	
Mobile vegetation – yes (n = 35)	14 (40%)	$P = 0.045$
Mobile vegetation – no (n = 82)	18 (22%)	

negative endocarditis). Demographic data are shown in Table 1 + *"5"*.

No differences in local structural complications were observed between both groups (Fig. 1). In relation to other complications, infection by *S. aureus* was significantly more associated with systemic embolism (41.7% vs 18.5%, $P = 0.01$), severe sepsis/septic shock (33.3% vs 3.7%, $P < 0.0001$) and in-hospital mortality (33.3% vs 12.3%, $P = 0.01$) (Fig. 2). In addition, patients in Group 1 had significantly higher incidence of brain embolism (30.6% vs 9.9%, $P = 0.01$). There was also a trend towards higher embolism of the spleen and kidney in Group 1 that did not reach statistical significance (Table 2). The mitral valve was the main source of embolism in both groups (46.7% vs. 66.7%).

The average length of vegetation in Group 1 was significantly higher (15.9 ± 8.6 mm vs 11.5±5.9 mm, $P = 0.02$). We did not, however, prove the relationship between the length and frequency of systemic embolism ($P = 0.43$). The biserial correlation coefficient was 0.09 in this case and, therefore, no correlation between these variables was demonstrated. On the contrary, we found a relationship between the mobility of vegetations and the frequency of embolism ($P = 0.045$) (Table 3).

Table 4. Logistic regression for in-hospital mortality, simultaneous embolism and severe sepsis/septic shock.

	OR (odds ratio)	95% confidence interval	*P*
Embolism	5.9	2.0 – 18.6	0.002
Severe sepsis/ septic shock	16.1	3.7 - 86.7	<0.001

Univariate statistical methods showed that significant risk factors for mortality in IE patients were due to infection by *S. aureus* (OR=2.9 and 95%CI=(1.1-7.3)), systemic embolism (OR=7.5 and 95%CI=(2.8-19.8)) and severe sepsis/septic shock (OR=18.8 and 95%CI=(5.2-68.0)). Using logistic regression, we simultaneously modelled the relationship between hospital mortality, embolism and severe sepsis/septic shock. Patients with embolism, regardless of the type of agent, had a 5.9x higher risk of hospital mortality compared with patients without embolism ($P = 0.002$). Subjects with severe sepsis/septic shock had a 16.1x higher risk of hospital mortality compared with patients without severe sepsis/septic shock ($P < 0.001$) (Table 4).

Table 5. Demographic data of the four major IE aetiological agents other than *S. aureus*.

	Coagulase-negative staphylococci (CNS)	Streptococci	Enterococci	Culture-negative
Number of patients/episodes of IE	16/17	16/16	12/15	18/21
Age (median)	64.7	49.4	58.2	65.3
Males/females	14/2	12/4	11/1	13/5
Aortic valve native/prosthesis	4 (23.5%) / 7 (41.2%)	12 (75 %) / 0	5 (33,3%) / 1(6,7%)	8 (38.1%) / 5 (23.8%)
Mitral valve native/prosthesis	3 (17.6%) / 0	4 (25%) / 0	12 (80%) /0	6 (28.6%) / 0
Tricuspid valve native/prosthesis	1 (5.9%) / 0	0/0	0/0	1 (4.8%) / 0
Implantable device/other	3 (17.6%) / 1 (5.9%)	0	0	1 (4.8%)
Cardiac surgery/ extraction of implanted device	5 (35.7%) / 3 (100%)	6 (37.5%)/0	4 (26,7 %) / 0	7 (35%) / 1 (100%)

Table 6. Comparison of complications in the *S. aureus* group with the groups composed of the four major aetiological agent-species.

	Staphylococcus aureus (n = 36)	Coagulase-negative staphylococci (n = 17)	Streptococci (n = 16)	Enterococci (n = 15)	Culture-negative endocarditis (n = 21)
Cardiac abscess	16.7% (6/36)	35.3% (6/17) ($P = 0.18$)	0% (0/16) ($P = 0.10$)	20% (3/15) ($P = 1$)	14.3% (3/21) ($P = 1$)
Valve perforation/prolapse	8.3% (3/36)	5.9 % (1/17) ($P = 1$)	31.3% (5/16) ($P = 0.09$)	13.3% (2/15) ($P = 0.62$)	19% (4/21) ($P = 0.40$)
AV conduction impairment	16.7% (6/36)	5.9% (1/17) ($P = 0.40$)	6.3% (1/16) ($P = 0.42$)	13.3% (2/15) ($P = 1$)	4.8% (1/21) ($P = 0.24$)
Heart failure	19.4% (7/36)	23.5% (4/17) ($P = 1$)	25% (4/16) ($P = 0.72$)	33.3% (5/15) ($P = 0.30$)	23.8% (5/21) ($P = 0.74$)
Systemic embolism	41.7%(15/36)	11.8% (2/17) ($P = 0.02$)	12.5%(2/16) ($P = 0.04$)	33.3% (5/15) ($P = 0.58$)	23.8% (5/21) ($P = 0.17$)
Severe sepsis/septic shock	33.3% (12/36)	5.9% (1/17) ($P = 0.04$)	0% (0/16) ($P = 0.01$)	6.7% (1/15) ($P = 0.08$)	4.8% (1/21) ($P = 0.02$)
In-hospital mortality	33.3% (12/36)	5.9%(1/17) ($P = 0.04$)	0% (0/16) ($P = 0.01$)	20% (3/15) ($P = 0.50$)	9.5%(2/21) ($P = 0.04$)

We also compared clinical courses, complications and outcomes between Group 1 (*S. aureus*) and four of the other most frequent pathogens (streptococci, enterococci, coagulase-negative staphylococci and culture-negative IE) separately (Table 6). No significant differences were found in the rate of local structural complications and/or in the incidence of complications between *S. aureus* and any other pathogen. There was a higher incidence of cardiac abscesses in IE caused by coagulase-negative staphylococci (CNS) when compared with the *S. aureus* group (35.3% vs 16.7%). Similarly, a higher rate of damage to the valvular apparatus was observed in the Streptococcus IE group in comparison with the *S. aureus* group (31.3% vs 8.3%). However, these differences were not statistically significant.

Importantly, *S. aureus* caused systemic embolism significantly more frequently than CNS (41.7% vs. 11.8%, $P = 0.02$) and streptococci (41.7% vs 12.5%, $P = 0.04$). In the *S. aureus* group, the incidence of severe sepsis/septic shock was very high and mortality rates were significantly higher than all other pathogens, except for enterococci (Table 4).

In the enterococcal group, a relatively high number of cardiac abscesses (20%) and heart failure episodes (33.3%) were observed. Together with the high incidence of systemic embolism (33%) and relatively high in-hospital mortality (20%), enterococcal IE indicated a very severe medical condition.

In the CNS group, the higher number of abscesses (35.3%) was presumably related to the high frequency of prosthetic endocarditis (58.8%).

Information about overall long-term survival probability was retrospectively obtained for all 85 patients (100%) who survived the acute phase of the IE episode. Long-term survival probability was significantly improved in patients with IE caused by agents other than *S. aureus* (13.78 median years vs 5.48 median years, $P = 0.03$). The annual distribution of IE episode diagnoses was not statistically significant between both groups ($P = 0.08$). None of the monitored selected variables were associated with decreased long-term survival estimates in the *S. aureus* group – cardiac abscess ($P = 0.97$), valve perforation/prolapse ($P = 0.82$), embolism ($P = 0.31$), AV conduction impairment ($P = 0.15$), heart failure ($P = 0.83$) and early surgery ($P = 0.14$).

DISCUSSION

S. aureus infection is currently the leading cause of IE in many regions of the world[7,8,10,15]. In addition to its high mortality figures, the frequency of *S. aureus* IE is on the increase and was recently estimated at between 25% and 50% (ref.[8,9,16]). It remains unclear whether the aggressiveness of IE is based more on local intracardiac damage or on systemic complications. Results of this study provide the most comprehensive analysis of IE-related complications in Central Europe.

In our study, we did not observe any significant differences in abscess formation, episodes of heart failure, AV conduction disorders or impairment of valve integrity during IE episodes involving *S. aureus* and other causes of IE. We proved that *S. aureus*, in comparison with other agents, causes significantly more septic embolism and severe sepsis/septic shock episodes. Systemic embolism occurs in 22% to 50% of IE cases and represents the highest risk of major cardiovascular events, including death[4]. In particular, cases of moderate-to-severe ischaemic stroke and brain haemorrhage were found to have a significant negative impact on the outcome of infective endocarditis[17].

Predicting an individual's risk of embolism is very difficult. Many studies have attempted to identify high-risk subgroups of patients with IE who could benefit from early surgery in order to prevent embolism. Some authors have reported an increased risk of embolisation episodes in patients with large vegetations[18-20], but others do not confirm this correlation[21-23]. In our study, the relationship between the length of vegetation and systemic embolism was not observed, but we did prove that high mobility of vegetation is an independent risk factor of embolism, which is in line with the most recently published data[18,20,24].

Two simple calculator systems for predicting embolic risk upon admission of patients with IE have been recently designed; one French[25] and one Italian[26]. Both include *S. aureus* infection as an excellent predictor of embolic risk. This is in accordance with our results, which suggest that *S. aureus* infection is, out of all the most common causative agents of IE, associated with the highest risk of systemic embolisation.

Reasons for increased incidence of embolism have been studied by Kupferwasser et al.[27]. They demonstrated that infections associated with elevated levels of antiphospholipid antibodies lead to the activation of endothelial cells, thrombin and reduced fibrinolysis. This cascade then leads to an increased risk of severe embolisation events. Therefore, an object of further study could be the relationship between levels of antiphospholipid antibodies and S. aureus infection, which may go some way to shedding light on its high embolic potential.

European guidelines on embolism-governing factors[28] are concerned with the size and mobility of vegetations, previous embolisms, the duration of antibiotic therapy and the types of microorganisms involved.

It is widely accepted that high mortality of patients with IE, especially of *S. aureus* origin, is mainly as a result of valvular apparatus impairment (leading to incipient heart failure and cardiogenic shock) (ref.[29]) or of severe sepsis leading to septic shock[30]. The latter scenario usually precludes referring the patient to surgery and is a predictor of highest mortality. Our data suggest a strong correlation between embolism and mortality. Systemic embolism represents the spread of infection on one side and the impairment of the target organ's function on the other, both of which lead to increased overall mortality.

Our results show that overall long-term survival probability is significantly improved in patients with IE when caused by agents other than *S. aureus*. The reason for this finding is unclear given that none of the selected variables

were associated with increased long-term mortality; therefore, further evaluation is required.

To conclude, infection with *S. aureus* needs to be unequivocally acknowledged as the highest risk of embolic complications and of short-term as well as long-term mortality in patients with IE. With respect to contemporary knowledge, the inclusion of *S. aureus* as an embolic risk factor should be incorporated in the guidelines for treatment of IE, given that in certain cases rapid indication for surgery of *S. aureus* IE is likely to decrease overall mortality[31]. This would be strongly beneficial in highlighting *S. aureus* as the predominant cause of IE in the 21st century[32,33]. However, additional prospective data are needed.

Study limitations

First, the retrospective nature of case identification and data acquisition did not allow for the complete ascertainment of patient information. Second, the study population included both native/prosthetic valve endocarditis and cardiac device infective endocarditis episodes in which the *S. aureus* group was compared with a group of mixed infectious agents (the most frequent aetiological agents). Third, with respect to our supposition that S. aureus infection is the predominant cause of IE in our cohort, and given that the types of complications related to IE episodes have not significantly changed over the past decade, we believe that the analysis of IE episodes from years 1998-2006 are in concordance with the present-day characteristics of the disease. Finally, the authors' unit serves as a referral centre for the management of more complicated cases, and thus the profile of the cases was most likely affected by referral bias.

CONCLUSIONS

Staphylococcus aureus infection represents the worst possible scenario for IE episodes, precipitating both increased short-term and long-term mortality. According to our data, high in-hospital mortality is caused by its systemic impacts and complications, especially by significantly higher incidence of systemic embolism and severe sepsis/septic shock.

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