Serious complications after infective endocarditis

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ORIGINAL ARTICLE

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ABSTRACT

INTRODUCTION: The objective of the present study was to review all cases of infective endocarditis at our hospital between 2002 and 2006 concerning the bacteriological aetiology and outcomes.

METHODS AND MATERIALS: This is a retrospective study based on medical records from patients in whom the discharge diagnosis infective endocarditis was established according to Duke's criteria. The study included 151 patients.

RESULTS: The most prominent risk factors were valvular prostheses (22%) and known valvular disease (21%). The median diagnostic delay was four days (0-103 days). The most prominent causative microorganism was *Staphylococcus aureus* (41%), followed by non-haemolytic streptococci (21%), haemolytic streptococci (10%) and enterococci (14%). The most frequently occurring complications were embolic events (29%) and valvular insufficiency (26%). Renal insufficiency, multi-organic failure and disseminated intravascular coagulation occurred in 36 patients (24%). Half of the patients (51%) received surgical treatment.

The overall in-hospital mortality was 29%, and 16% had severe sequelae at discharge. High mortality was found, particularly in the elderly patients, in patients who had staphylococcal endocarditis and in patients with valvular prosthesis.

CONCLUSION: Despite considerable progress in diagnostics and treatment facilities, infective endocarditis remains a serious disease with long diagnostic delay times, high complication rates and a high mortality.

Infective endocarditis (IE) is a severe disease with persistent, high morbidity and mortality, even though patients are treated according to current guidelines as recommended by the European Society of Cardiology and the Danish Society of Cardiology [1, 2]. The aim of this study was to review all cases of definite or suspected IE at our hospital in the period from January 2002 to December 2006. Causative microorganisms, diagnostic delay times, complications and clinical outcomes of IE were studied. Furthermore, the purpose was to compare these findings with earlier surveys.

MATERIAL AND METHODS

This retrospective study was based on medical records from patients who were discharged with the diagnosis IE in the above-mentioned five-year period from the Departments of Cardiology, Internal Medicine and Thoracic Surgery at Odense University Hospital, Denmark. Only patients diagnosed with definite and suspected IE according to Duke's criteria were included [3].

Diagnostic delay was defined as the time from admission until the date when the diagnosis was confirmed. Echocardiography was performed in all patients. Surgery was defined as acute when the operation was performed on the same day as the diagnosis was made, and as subacute when surgery was performed within 1-7 days after the day of the diagnosis.

STATISTICS

For data analysis, the SPSS software (Statistical Package for the Social Science) was used. Only descriptive analyses were performed.

ETHICS

The study was approved by the Danish Data Protection Agency.

RESULTS

A total of 151 patients were admitted for definite (N=128) or suspected (N=23) IE at our hospital. Two patients had recurrent endocarditis. The patients' age and sex distribution is shown in **Table 1**. The median age was 70 years.

Portal of entry

Despite intensive investigation, the portal of entry remained unknown in 42 cases (27%). Oral entry was suggested in 21%, entry via the skin in 20%, entry via the urinary tract in 10%, entry via the lungs in 7%, entry via bone or joints in 7% and entry via the intestines in 4%. In the remaining 7%, entry was possibly via intravenous catheters and other foreign bodies, including a pacemaker and an implantable cardioverter defibrillator.

Interestingly, among patients with previous valvular surgery, oral entry was only verified in one out of 33 patients (3%), whereas oral entry was found in 31 (26%) patients without previous valve surgery.

Diagnostic delays

The diagnostic delays varied widely from 0 to 103 days (median four days). One hundred and five cases (68%) were diagnosed within seven days from admission.

TABLE 1

Age and gender distribution.

	2002	2003	2004	2005	2006	Total
Incidence, n	29	34	25	37	26	151
Age, years, median (range)	63 (35-85)	75 (35-91)	60 (30-85)	65 (20-90)	70 (30-80)	70
Male/female, n	15/14	24/10	15/10	29/8	16/10	99/52

n = number

TABLE 2

Affected valves.

	n (%)	Surgery, n	In hospital mortality, n (% of the group)
Native aortic	59 (39)	35	13 (22)
Prosthetic aortic	20 (13)	10	11 (55)
Native mitral	29 (19)	12	7 (24)
Prosthetic mitral	4 (3)	1	2 (50)
Tricuspid	9 (6)	1	0 (0)
Serveral valves affected[a]	10 (6)	5	7 (70)
Non found	20 (14)	0	4 (20)
Total	151 (100)	64	44 (29)

Among the remaining 46 cases, 23 cases were registered as possible IE at discharge. A long diagnostic delay appeared to be independent of predisposing factors.

Affected valves

Table 2 lists the affected valves and the related outcome. Transthoracic echocardiography (TTE) and/or transoesophageal echocardiography (TOE) revealed clear signs of IE in 118 patients (78%) (**Figure 1**). Remarkably, four out of 34 patients with a prosthetic valve had IE at their native valve.

Bacteriology

Blood culture yielded a positive result in 141 cases (93%). In one patient with fulminant disease, no attempt was made to obtain blood for culture. **Table 3** shows the spectrum of the infective microorganisms. In this study, 62 patients (41%) were affected by *Staphylococcus aureus* and 47 patients (31%) were affected by streptococci.

Complications

Cardiac complications caused by IE were registered in 113 patients (74%). Valvular insufficiency was the most prominent cardiac complication (26%) followed by paravalvular leakage (13%) and heart failure secondary to valvular insufficiency (9%).

Non-cardiac complications occurred in 86 patients (56%); 44 experienced cerebral or/and peripheral embolism, six suffered from cerebral or/and peripheral abscess, while renal insufficiency occurred in 20 patients, multi-organ failure in 14 and disseminated intravascular coagulation in two. Among 86 cases with non-cardiac complications, 17 were discharged with severe sequelae, and 36 patients died.

Complications to IE varied between the various causative microorganisms. Among the most frequent microorganisms, non-cardiac complications occurred in 62% of staphylococcal IE and in 45% of streptococcal IE.

Surgery

As shown in Table 2, valvular surgery was performed in 64 out of the 128 well-defined IE (50%) cases. The age of the patients who received surgery ranged from 16 to 82 years (median 59 years). Emergency surgical intervention was required in six patients due to severe cardiac complications. Subacute surgical intervention was performed in 24 patients. Among 64 operations, seven valvular reconstructions were performed, and 18 biological and 33 mechanical artificial valves and six homografts were implanted.

Outcomes

Of the 151 admitted patients, 83 were discharged without any sequelae (54%), 19 of these had possible IE and 64 had well-defined IE (50% of patients with well-defined IE).

Twenty-four cases (16%) were discharged with sequelae such as hemiparesis, amputated leg, or cardiac or renal failure. We registered 44 deaths (29%). Among the 128 well-defined IE, the in-hospital mortality was 34%.

In the younger age-group, we registered 12 deaths (mortality 15%). In the older age group, 32 deaths were registered (mortality 47%). Mortality rates were identical for males and females.

The mortality rates varied between the different IE localisations as shown in Table 2. The worst prognosis was seen in patients with a prosthetic valve and in patients in whom several valves were affected. Remarkably, a 20% mortality was registered in patients in whom no signs of IE could be visualised by echocardiography. We documented no relationship between diagnostic delays and outcomes.

The various causative microorganisms were related to different outcomes, as illustrated in Table 3. The mortality rate was markedly lower in the group who received surgical treatment (14%) than in the group who received antibiotics alone (40%). However, the groups were not comparable due to different baseline characteristics.

DISCUSSION

The past three decades have seen several reviews on IE from different parts of the world. They have had different purposes and different variables have been registered. Some reviewed only native valve endocarditis [4], others focused on nosocomial infective endocarditis [5] and several [6-15] had the same focus as our survey. Regardless of their differences, these reviews illustrate a persistent pattern in IE and that alterations over time are, indeed, small.

Age

Our study population's age ranged from 16 to 91 years which resembled the ranges recorded in previous reviews [4, 9, 12-14]. Aging is associated with an increased risk of cardiac disease, which is the most common predisposing factor for IE. Conversely, IE can affect patients in any age group and the wide age span may lie at the root of the diagnostic challenges in IE.

Portal of entry

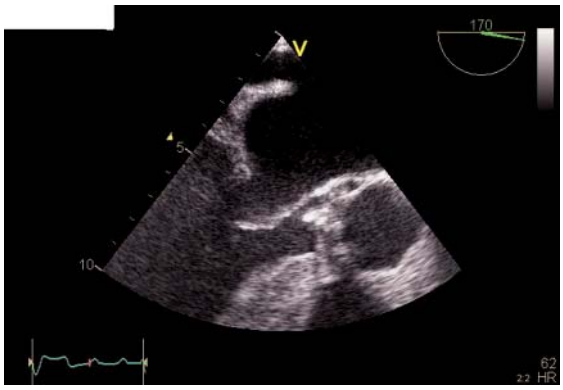
Of 33 cases with previous valve surgery, only one was registered in which a dental focus was suggested as the portal of entry. This is a very low figure compared with patients with native valve IE in whom a dental focus was suggested in 32% of cases. The reason for this difference may be that all patients with planned valve surgery in our region were evaluated for a possible infectious reservoir by hospital odontologists. Therefore, we suggest that this regime should continue as a prophylactic therapy.

Diagnostic delays

The median diagnostic delay for IE in our study was four days as opposed to five days in a study on native IE in the same region 15 years ago [4], and eight days observed in a recent European study [8]. Interestingly, the diagnostic delay did not become shorter over time despite the introduction of diagnostic tools like echocardiography and microbiologic culturing, and despite the considerable experience held by physicians at our University Hospital. The present study showed no trend towards increased complication rates or mortality among the cases in whom the diagnosis was delayed for more than seven days. One reason for this may be a substantial selection bias, as patients with fulminant disease may be diagnosed easier and earlier.

FIGURE 1

Transoesophageal echocardiography: infective endocarditis at a native aortic valve.



Causative microorganism

Table 4 shows the incidence of the most prominent causative micro-organisms in earlier surveys and in our study. In the present study, 41% had *Staphylococcus aureus* IE compared with 16-34% in previous Danish

TABLE 3

Causative microorganisms, affected valves and related mortality.

	Frequency n, (%)	Native aorta, n	Native mitral, n	Prosthesis, n	Tricuspid, n	Several valves[a], n	Location unknown, n	Mortality, n (%)
Staphylococcus aureus	62 (38)	17	15	12	7	4	7	24 (39)
Other staphylococci	5 (3)	3		1			1	2 (40)
Non-haemolytic streptococci	32 (21)	19	5	3	1	1	3	7 (21)
Haemolytic streptococci	15 (10)	7	4	2	1		1	2 (13)
Enterococci	21 (14)	7	2	3		3	6	5 (24)
Haemophilus species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* species and *Kingella*	3 (2)	2				1		0 (0)
Fungi	1 (1)			1				1 (100)
Escherichia coli	2 (1)		2					1 (50)
Negative culture	9 (6)	4	1	1		1	2	1 (11)
No culture	1 (1)						1	1 (100)
Total	151 (100)	59	29	24	9	10	20	44 (29)

a) Several valves included both native and prosthetic valves.

TABLE 4

Most prominent causative microorganisms and mortality in different surveys.

	Streptococcus viridans, %	Staphylococcus aureus, %	Mortality, %
Nissen et al, 1992 [4]	21	28	33
Benn et al, 1997 [16]	21	34	36
Hoen et al, 2002 [6]	17	17	16
Krcmery et al, 2003 [7]	15	29	
Foghsgaard et al, 2004 [17]	34	16	14
Chu et al, 2004 [9]	34	16	20
Cecchi et al, 2004 [8]	25	31	14
Loupa et al, 2004 [10]	18	34	16
Ferreiros et al, 2006 [12]	21	23	25
Walpot et al, 2006 [14]	27	30	
Tleyjeh et al, 2007 [20]	44	33	26
Le & Grill, 2010 (this study)	21	41	29

studies [4, 16, 17] and 22-34% in studies performed in other European countries, New Zealand and Argentina [6-10, 12-14]. This suggests a slight increase in the proportion of staphylococcal IE. We wonder if increased use of invasive medical procedures such as arthroscopy and endoscope surgery may explain the increased incidence of staphylococcal IE, but this study cannot answer such a question. About 38% of our patients had invasive medical procedures performed shortly before their IE, but the microbiological findings in those patients showed no clear trend.

Antibiotic prophylaxis

We did not register whether antibiotic prophylaxis prior to invasive procedures had been used by our patients. In the period covered by this survey, the Danish Society of Cardiology recommended the administration of prophylactic antibiotics prior to performing specific medical procedures, e.g. in the oral cavity, respiratory organs, piercing or tattoos, in patients with a high/moderate risk [2]. Seto TB [18] studied the effect of infectious endocarditis prophylaxis, and concluded that no study has definitively determined whether prophylactic antibiotics may prevent IE in humans – although studies suggested that prophylactic antibiotics may decrease the risk of procedure-related endocarditis. As a consequence, in 2009, the European Society of Cardiology published more simplified and restrictive guidelines for the prevention of infective endocarditis [19]. The future will show whether these guidelines will result in larger numbers of procedure-related IE, or whether the amount of patients with IE will remain unchanged.

Complications

IE is a severe infection characterised by a high incidence of both cardiac and non-cardiac complications, and it is associated with a poor prognosis. In our study, 65 patients had cardiac as well as non-cardiac complications, and 30 of these patients died during the hospital stay. Among the remaining 14 deaths observed in our study, either cardiac or non-cardiac complications were registered. Severe non-cardiac complications were found more frequently in cases with staphylococcal IE than in cases with streptococcal IE (62% versus 45%). This characteristic of staphylococcal IE was also reported in a previous Danish study [4].

Outcomes

The outcome of IE was related to the causative microorganisms. Among the most common microorganisms, staphylococcal endocarditis had the highest mortality rate (38%), which is in line with results from previous studies where the mortality rates for this group of patients varied from 38% to 69% [4, 8, 9, 11]. The mortality rate was 19% for patients with streptococci endocarditis.

Surgery was performed in 51% of the patients in our study compared with 14% in a study from 1992 [4] and 21-49% in other studies from this decade [6, 8, 9, 12-14, 17]. Consequently, there may be a trend towards more surgical treatment in IE [20]. Another reason for the higher surgery rates of our study was its highly selected population as our hospital department serves as a referral centre and some patients were referred directly to the thoracic surgery department. Patients who received valvular surgery had a significantly lower mortality (14%) than non-operable patients (40%). The reason may be that the median age of surgically treated patients was 59 years, whereas the median age of patients treated with antibiotics alone was 72 years.

Consequently, the occurrence of IE co-morbidity in the two groups was not comparable. This study cannot answer the question whether the mortality rates could have been improved if more of the elderly patients had received surgery. The overall in-hospital mortality in our study was comparable to that of other studies (29% versus 14-35%) [4, 6-13, 16]. Every third patient with a well-defined IE died from the disease, and the mortality was highest in the elderly patient group (47% versus 15%). Patients with prosthesis endocarditis had a more severe prognosis (54%) than those who had native valve endocarditis (20%), although the patients had the same median age.

In conclusion, the mortality among IE patients remains elevated, and we found no trend towards a mortality decrease over time.

Limitations of the study

The number of patients in our study was lower than expected according to the known incidences, about 100

cases per million. The estimated incidence for our region should be about 100 patients a year. As we only found 30 patients a year, a considerable number of patients were not registered. The population in our study is a mix of highly selected and unselected patients. Some patients were directly referred to the Department of Thoracic Surgery. Naturally, these hospitals did not refer non-operable patients. So the results of our study are not directly comparable to those reported in other reviews. Our data were collected retrospectively, and some data were missing. Bias may also arise if patients were incorrectly registered.

CONCLUSION

Our study illustrates that the diagnostic delay times for IE remain high and have remained almost unchanged during the past three decades. This illustrates the persistent diagnostic challenge in IE which is rooted in its varied and often unspecific symptomatology. An early start of specific antibiotic and surgical therapy may prevent complications and thereby improve the prognosis of IE patients. The incidence of IE with *Staphylococcus aureus* follows an increasing trend with ensuing high morbidity and mortality.

IE was associated with a persistently high mortality, especially for elderly patients and for patients with prosthetic valves. Odontological evaluation may have a persistent and important prophylactic role in valvular surgery.

An increase in IE surgery rates may have the potential to improve the prognosis, but no randomised studies exist to confirm such statement.

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