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INFECTIVE ENDOCARDITIS IN A FINNISH TEACHING HOSPITAL

25 Years of Experience of Adult Patients

by

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to my family

ABSTRACT

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Infective endocarditis in a Finnish Teaching Hospital: 25 years of experience of adult patients
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Annales Universitatis Turkuensis
Painosalama OY, Turku, Finland 2007

Background: Infective endocarditis (IE) is a serious disease. Despite major advances in diagnosis and therapy, morbidity and mortality associated with IE are high. Recently, considerable changes in the clinical pattern of IE have occurred in many countries.

Aims: This study was performed to evaluate the clinical presentation and outcome of adult patients with IE treated in a Finnish teaching hospital between 1980 and 2004.

Methods: In Study I, 243 consecutive episodes of suspected IE in 222 patients treated between 1980 and 1995 were retrospectively evaluated for the likelihood of IE, the Duke and the von Reyn diagnostic criteria were used. In Study II, IE-associated neurological complications were analyzed in 218 episodes of definite or possible IE, with emphasis on comparison between patients with and without neurological symptoms. In Study III, the diagnostic usefulness of serial serum C-reactive protein (CRP) measurements in monitoring the outcome of IE in 134 episodes of definite IE was assessed. In Study IV, broad-range bacterial rDNA PCR followed by sequencing was applied to analyze valve samples from 56 patients operated on for diagnosed or suspected IE. In Studies V and VI, 326 episodes of IE in 303 patients treated during 1980-2004 were evaluated for short-term outcome, 1-year outcome, clinical characteristics of IE and changes of clinical characteristics over time.

Results: The Duke criteria were more sensitive than the von Reyn criteria to diagnose IE. Of the 243 episodes evaluated, 114 were designated as definite IE by the Duke criteria, as compared with 64 episodes by the von Reyn criteria ($p<0.001$). As many as 115 disease episodes were rejected by the von Reyn criteria, whereas only 37 episodes were rejected by the Duke criteria ($p<0.001$). The neurological manifestations, when present, were evident before antimicrobial treatment in 76% of episodes and were the first sign of IE in 47% of episodes. There was a significant association between neurological complications and death. The fall in serum CRP was significantly faster when recovery was uncomplicated than when complications developed or death ensued. In surgically treated patients, PCR was the only method to provide the etiological diagnosis in 4 patients (2 *Staphylococcus* species, 1 *Streptococcus bovis*, 1 *Bartonella quintana*); all had received antimicrobials before blood cultures were taken. Overall in-hospital and 1-year mortality were predicted by infection of 2 native valves, the occurrence of neurological complications, the occurrence of peripheral emboli, and heart failure. Death within 1 year was associated with age ≥65 years and the presence of a major criterion or vegetation on echocardiography. There was a significant trend between the level of serum CRP on admission and the short-term outcome and 1-year outcome. Episodes associated with intravenous drug use (IVDU) increased significantly over 25 years ($p<0.001$).

Conclusions: The Duke criteria are valid for diagnosing IE. The results support the conclusion that rapid diagnosis and institution of antimicrobial therapy may be the most effective means to prevent neurological complications and to improve prognosis. Normalization of CRP was a good predictor of a favorable late outcome. PCR of samples from the removed valve tissue was useful for identifying the causative agent, if it was fastidious or if the specimen was taken during antimicrobial treatment. Regarding outcome, some factors predicting a poor prognosis were the same as in previous studies; a new finding was that high CRP values on admission predict significantly short-term and 1-year mortality. The emergence of IVDU-associated episodes was the major change in the clinical pattern of IE during this 25-year study period.

Keywords: Infective endocarditis, neurological complications, prognosis, CRP, PCR

TIIVISTELMÄ

Maija Heiro

Infektiivinen endokardiitti yliopistollisessa keskussairaalassa vuosina 1980-2004 hoidetuilla aikuispotilailla

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Turun yliopiston julkaisuja
Painosalama OY, Turku, Suomi 2007

Tausta: Infektiivinen endokardiitti on edelleen vakava sairaus. Huolimatta siitä, että taudin diagnostiikka ja hoito ovat kehittyneet, siihen liittyy edelleen merkittävää sairastuvuutta ja kuolleisuutta. Endokardiitin taudinkuvassa on viime vuosina tapahtunut muutoksia monissa maissa.

Tavoitteet: Tutkia endokardiitin kliinista kuvaa ja ennustetta suomalaisessa yliopistosairaalassa vuosina 1980-2004 endokardiitin vuoksi hoidetuilla aikuispotilailla.

Aineisto: Osatyössä I endokardiitin todennäköisyyttä analysoitiin 222:lla vuosina 1980-1995 endokardiittiepäilyn vuoksi hoidetulla potilaalla käyttäen apuna sekä Duken että von Reyn diagnostisia kriteereitä. Osatyössä II tutkittiin endokardiittiin liittyviä neurologisia komplikaatioita 218 varmassa tai mahdollisessa endokardiittiepisodissa. Osatyössä III tutkittiin seerumin C-reaktiivisen proteiinin (CRP) käyttökelpoisuutta hoitovasteen arvioinnissa 134:ssä varmaksi luokitellussa endokardiittiepisodissa. Osatyössä IV tutkittiin yleisbakteeri-PCR-menetelmän käyttökelpoisuutta etiologisessa diagnostiikassa 56:lla endokardiittiepäilyn vuoksi leikatulla potilaalla. Osatöissä V ja VI analysoitiin kaikki vuosina 1980-2004 hoidetut 303 endokardiittipotilasta lyhytaikais- ja 1-vuotisennusteen suhteen sekä tutkittiin endokardiitin taudinkuvassa tapahtuneita muutoksia sairaalassamme.

Tulokset: Duken kriteerit osoittautuivat von Reyn kriteereitä herkemmiksi endokardiitin diagnostiikassa: 243 tutkitusta episodista 114 luokiteltiin varmoiksi endokardiiteiksi Duken kriteereillä, kun vastaavasti ainoastaan 64 luoteltiin varmoiksi von Reyn kriteereillä ($p<0.001$). Lisäksi peräti 115 episodissa endokardiitin diagnoosi hylättiin von Reyn kriteereillä, kun diagnoosi hylättiin Duken kriteereillä ainoastaan 37 episodissa ($p<0.001$). Neurologinen komplikaatio ilmeni ennen mikrobilääkehoidon aloittamista 76 %:ssa episodeja ollen ensimmäinen oire 47 %:ssa. Kuolema oli merkitsevästi yhteydessä neurologisiin komplikaatioihin. Hoitovastetta seurattaessa seerumin CRP:n lasku oli merkitsevästi nopeampaa komplikaatioitta toipuvilla potilailla kuin niillä, joille kehittyi komplikaatioita tai jotka menehtyivät tautiinsa. PCR-tutkimus poistetusta läpästä antoi ainoana menetelmänä etiologisen diagnoosin neljässä tapauksessa (2 stafylokokkilajia, 1 *Streptococcus bovis*, 1 *Bartonella quintana*), joissa kaikissa mikrobilääkehoito oli ollut käytössä ennen näytteiden ottamista. Koko aineistossa kahden läpän infektio tai neurologisten komplikaatioiden, perifeeristen embolioiden tai sydämen vajaatoiminnan kehittyminen ennustivat sekä sairaalakuolleisuutta että 1-vuotiskuolleisuutta, kun taas ≥65 vuoden ikä ja sydämen ultraäänitutkimuksessa todettu vegetaatio tai Duken luokittelun mukainen pääkriteeri ennustivat kuolemaa vuoden sisällä. Korkea CRP-taso sairaalaan tullessa ennusti sekä sairaalakuolleisuutta että 1-vuotiskuolleisuutta. Huumeiden käyttäjien endokardiitit lisääntyivät tutkimusaikana merkitsevästi ($p<0.001$).

Päätelmät: Tässä työssä vahvistetaan Duken kriteerien käyttökelpoisuus endokardiitin diagnostiikassa. Lisäksi vahvistui käsitys, että nopea diagnoosi ja mikrobilääkehoidon aloittaminen ovat parhaat keinot ehkäistä neurologisia komplikaatioita ja parantaa endokardiittipotilaiden ennustetta. CRP:n normalisoituminen on endokardiittipotilailla hyvän ennusteen merkki. Suoraan läppäkudoksesta tehty PCR-tutkimus on hyödyllinen, kun taudin aiheuttaja on kasvuominaisuuksiltaan vaativa tai potilas on saanut mikrobilääkehoitoa ennen viljelynäytteiden ottamista. Muutamat aiemmissa tutkimuksissa todetut huonon ennusteen merkit ennustavat huonoa ennustetta myös tämän tutkimuksen potilailla. Uutena löydöksenä ilmeni, että korkea CRP-arvo sairaalaan tullessa merkitsee sekä huonoa lyhyt- että pitkäaikaisennustetta. Huumeiden käyttäjien endokardiittien ilmaantuminen on tärkein epidemiologinen muutos 25 vuoden tutkimusaikana.

Avainsanat: Infektiivinen endokardiitti, neurologiset komplikaatiot, ennuste, CRP, PCR

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ABBREVIATIONS

AG	aminoglycoside
CHF	congestive heart failure
CNS	central nervous system
CHD	congenital heart disease
CRP	C-reactive protein
CT	computed tomography
ECG	electrocardiography
ESR	erythrocyte sedimentation rate
GN	glomerulonephritis
IE	infective endocarditis
i.v.	intravenous
IVDU	intravenous drug use
MIC	minimum inhibitory concentration
MRI	magnetic resonance imaging
NVE	native valve endocarditis
PCR	polymerase chain reaction
PVE	prosthetic valve endocarditis
spp.	species
TEE	transesophageal echocardiography
TTE	transthoracic echocardiography
WBC	white blood cell

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, which are referred to in the text by the Roman numerals I-VI.

I Heiro M., Nikoskelainen J., Hartiala J., Saraste M., Kotilainen P. Diagnosis of infective endocarditis. Sensitivity of the Duke vs von Reyn criteria. *Arch Intern Med* 1998;158:18-24.

II Heiro M., Nikoskelainen J., Engblom E., Kotilainen E., Marttila R., Kotilainen P. Neurologic manifestations of infective endocarditis: a 17-year experience in a teaching hospital in Finland. *Arch Intern Med* 2000;160:2781-7.

III Heiro M., Helenius H., Sundell J., Koskinen P., Engblom E., Nikoskelainen J., Kotilainen P. Utility of serum C-reactive protein in assessing the outcome of infective endocarditis. *Eur Heart J* 2005;26:1873-81.

IV Kotilainen, P., Heiro M., Jalava J., Rantakokko V., Nikoskelainen J., Nikkari S., Rantakokko-Jalava K. Aetiological diagnosis of infective endocarditis by direct amplification of rRNA genes from surgically removed valve tissue. An 11-year experience in a Finnish teaching hospital. *Ann Med* 2006;38:263-73.

V Heiro, M., Helenius H., Hurme S., Savunen T., Engblom E., Nikoskelainen J., Kotilainen P. Short term and one-year outcome of infective endocarditis in adult patients treated in a Finnish teaching hospital during 1980-2004. *BMC Infect Dis* 2007;7:78.

VI Heiro M., Helenius H., Mäkilä S., Hohenthal U., Savunen T., Engblom E., Nikoskelainen J., Kotilainen P. Infective endocarditis in a Finnish teaching hospital: a study on 326 episodes treated during 1980-2004. *Heart* 2006;92:1457-62.

1. INTRODUCTION

Infective endocarditis (IE) is a serious disease which in the preantibiotic era was always fatal. Despite improvements in population health and health care, the incidence of IE (1.7-6.2 per 100 000 patient years) has not chanced over the past 2 decades. (Mylonakis and Calderwood 2001)

Clinicians treating patients with IE have faced a varying pattern of the disease. The risk factors, causative microorganisms and the age of the patients have changed. Mitral valve prolapse, degenerative valve disorders and prosthetic valves have replaced chronic rheumatic heart disease as the most common cardiac condition predisposing to IE in the occidental industrialized world. (Cabell and Abrutyn 2003) Furthermore, the number of patients without previously diagnosed heart disease has increased. (Hoen, Alla et al. 2002) New risk factors, such as intravenous drug use (IVDU), long term hemodialysis, and nosocomial disease have emerged over the years, and the age of the patients with non-IVDU endocarditis has increased. (Moreillon and Que 2004)

Classically, the predominant causative agent has been the viridans streptococcus, which causes the subacute (lenta) type of endocarditis. However, in many recently described patient populations, the most frequently isolated microorganism has been *Staphylococcus aureus*, manifested clinically as acute endocarditis. (Cabell, Jollis et al. 2002) Fever may be the only symptom and the classical signs of subacute IE are missing. Congestive heart failure (CHF) complicates more than half of all episodes and it is the leading cause of death among IE patients. (Sexton and Spelman 2003) The second most common complication of IE is embolism, which occurs in about 40% of the IE patients. (Hogevik, Olaison et al. 1995) Frequently, IE embolism involves the central nervous system (CNS) with subsequent neurological complications and results in significant morbidity and mortality.

IE is a diagnostic and therapeutic challenge to clinicians. Due to the highly variable clinical presentation of IE, different sets of diagnostic criteria have been used to direct and standardize case definitions, both in clinical and scientific work. Today, the Duke criteria (Durack, Lukes et al. 1994) presented in 1994 and subsequent modifications are considered to be the most accurate. Their major advantage compared to the older von Reyn classification (Von Reyn, Levy et al. 1981) is the inclusion of certain echocardiographic findings as major criteria and the inclusion of IVDU as a predisposing condition of IE. In up to 10-14% of IE, blood cultures are negative due to previous antibiotic therapy or because of fastidious or non-culturable microbes. (Hoen, Selton-Suty et al. 1995) In these situations, the polymerase chain reaction (PCR) approach has proved to be useful. (Goldenberger, Kunzli et al. 1997) The technique can identify bacterial DNA directly from excised valvular material or from distant emboli regardless of antimicrobial treatment.

Despite major advances in cardiac imaging, antimicrobial treatment and surgical techniques, the morbidity and mortality associated with IE remain high. In recent series, 1-year mortalities of 25-40% have been reported. (Cabell, Jollis et al. 2002;

Thuny, Di Salvo et al. 2005) In IE, careful follow-up of the efficacy of treatment is particularly important to insure medical cure and optimal timing of surgery. The clinical usefulness of serial serum C-reactive protein (CRP) measurements in monitoring the response to therapy in patients with septicemia and bacterial meningitis is well documented. (Yentis, Soni et al. 1995) However, only a few studies have focused on the value of CRP in IE. (Hogevik, Olaison et al. 1997; Olaison, Hogevik et al. 1997)

In the present study, we have evaluated the clinical presentation, presence of neurological manifestations and short-term and 1-year clinical outcome of patients treated for IE in a Finnish teaching hospital between 1980 and 2004. We have also compared the von Reyn and the Duke criteria for evaluation of the likelihood of IE and focused on the usefulness of the PCR amplification for establishing the causative agent of IE. Finally, we have examined the usefulness of CRP and other markers of inflammation in assessing the outcome of patients with IE.

2. REVIEW OF THE LITERATURE

2.1. Epidemiology of infective endocarditis (IE)

The incidence of IE in the United States and western Europe is 1.7 to 6.2 cases per 100 000 patient years (Delahaye, Goulet et al. 1995; Hoen, Selton-Suty et al. 1995; Hogevik, Olaison et al. 1995; Mylonakis and Calderwood 2001; Hoen, Alla et al. 2002), but it can be higher in urban populations. (Berlin, Abrutyn et al. 1995) In a review of 26 publications and 3784 episodes of IE between 1993 and 2003, Moreillon and Que reported a median incidence of IE of 3.6 per 100 000 individuals per year with a clear increase with age: ≤5 episodes and ≥15 episodes per 100 000 individuals per year in subjects younger than 50 years and older than 65 years, respectively. (Moreillon and Que 2004) It is estimated that the incidence of IE is 4 to 6 times higher in elderly than young people. (Nissen, Nielsen et al. 1992; Delahaye, Goulet et al. 1995)

Despite improvements in population health and health care, the incidence of IE has not changed over the past 2 decades (Watanakunakorn and Burkert 1993; Sandre and Shafran 1996; Mylonakis and Calderwood 2001; Hoen, Alla et al. 2002; Devlin, Andrews et al. 2004; Tornos 2005), which is due to a progressive change in IE risk factors. Chronic rheumatic heart disease, which was the prime risk factor in the pre-antibiotic era, is now rare in industrialized countries. (McKinsey, Ratts et al. 1987) This group has been replaced by new at-risk groups, including patients with IVDU, elderly people with sclerotic valves, patients with valve replacement or vascular instrumentation, hemodialysis patients and patients exposed to intensive care and immunosuppressive medication. (Gouello, Asfar et al. 2000; Bouza, Menasalvas et al. 2001; Abbott and Agodoa 2002; Cabell, Jollis et al. 2002; Cabell and Abrutyn 2003) These changes explain the growing incidence of staphylococcal infections and infections caused by pathogens that are not easily detected by usual blood cultures. (Roder, Wandall et al. 1999; Fowler, Miro et al. 2005) Previously undetected pathogens are now being identified in connection with IE, and multidrug-resistant bacteria challenge conventional treatment regimens. (Moreillon and Que 2004) The widespread use of echocardiography has probably also increased the rate of IE diagnoses. Some features of recent series of endocarditis are shown in **Table 1**.

The median age of patients with IE has gradually increased; it was 30-40 years during the preantibiotic era and is 47-69 years more recently. (Watanakunakorn and Burkert 1993; Hogevik, Olaison et al. 1995) In contast, IE associated with IVDU occurs in younger persons. Among IE patients, men are more often affected than women at a mean male-to-female ratio of 1.7-2.1:1. (Mouly, Ruimy et al. 2002; Devlin, Andrews et al. 2004)

Table 1. Features of infective endocarditis reported since the 1990's

First author, year	N	Mean age, years	PVE (%)	IVDU (%)	Viridans streptococci / *Staph. aureus* / enterococci (%)	Early surgery (%)	In-hospital mortality (%)	Country
Watanakunakorn, 1993	210	60-70*	14	17	14 / 47 / 5	14	21	USA
Durack, 1994	204	48	15	28	23 / 37 / 7	37	21	USA
Delahaye, 1995	415	56	22	5	27 / 18 / 9	13	24	France
Hogevik, 1995	127	62	15	7	28 / 31 / 6	15	13	Sweden
Sandre, 1996	135	49	30	11	27 / 27 / 6	33	19	Canada
Cabell, 2002	329	57	30	8	11 / 40 / 10	NG§	16†	USA
Fefer, 2002	108	57	31	NG§	31 / 13 / 11	18	11	Israel
Hoen, 2002	390	60	16	6	17 / 23 / 8	49	16	France
Netzer, 2002	212	51	17	10	32 / 23 / NG§	38	15	Switzerland
Wallace 2002	208	52	32	9	25 / 23 / 11	51	18	England
Chu, 2004	267	58	18	6	10 / 44 / 9	27	19	USA
Tornos, 2004	159	57	26	5	13 / 33 / 14	39	13	Europe‡
Thuny, 2005	384	57	24	6	25 / /21 / 7	52	10	France

* Median ages
§ Not given
† Mortality within 30 days
‡ 92 centers from 25 European countries

2.2. Pathogenesis of IE

An initial mechanical trauma to the endocardial lining is possibly initiated by aberrant jet streams in the blood flow passing through diseased heart valves. At first, a direct contact between blood and subendothelial components results in platelet and fibrin deposition forming a coagulum. Pathogens associated with IE circulating in the bloodstream, as a result of transient bacteremia, adhere to the coagulum and in turn attract and activate monocytes to produce cytokines, resulting in progressive enlargement of the infected coagulum, formally named vegetation. (Crawford and Russell 1986; Veltrop, Bancsi et al. 2000; Moreillon, Que et al. 2002) The adherence of microorganisms is mediated by microbial surface components recognizing adhesive matrix molecules (MSCRAMMS). (Patti and Hook 1994) The endothelial cells, fibroblasts, and platelets produce fibronectin facilitating adherence of the infectious agents to the vegetation. Certain organisms, e.g. *Staph. aureus* and a few other associated pathogens, carry receptors for adhesive proteins on their surface. (Moreillon, Que et al. 2002) Once adhered, the infecting microorganisms can survive by avoiding host defences and this results in local extension, tissue damage and spread to distant organs. (Sinha, Francois et al. 2000; Kreikemeyer, Klenk et al. 2004)

Valve inflammation can arise in several clinically silent situations. For instance, up to 25% of patients above 40 years have degenerative valve lesions that harbor microulcerations and local inflammation, resembling arteriosclerosis. (McKinsey, Ratts et al. 1987; Stehbens, Delahunt et al. 2000) Staphylococcal endocarditis occurs often among patients with previously healthy valves, and microulcerations are thought to be responsible for endocarditis by this mechanism. Similarly, repeated injections of impure material by persons with IVDU could encourage bacterial adherence (particularly *Staph. aureus*) by stimulating MSCRAMMs on normal heart valves. (Moreillon, Que et al. 2002) This is probably the cause of tricuspid valve IE

predominance among drug addicts, since in other patient populations right-sided IE is uncommon. Other hypotheses on the development of IE associated with IVDU include cocaine-induced microtrombi on the cardiac valves, drug-induced pulmonary hypertension with increased right-sided intracardiac turbulence, and HIV-infection. (Frontera and Gradon 2000)

2.3. Risk factors of IE

2.3.1. Cardiac

About 75% of all patients with endocarditis have some pre-existing structural abnormality of the affected cardiac valve. (McKinsey, Ratts et al. 1987; Steckelberg and Wilson 1993; Dajani, Taubert et al. 1997) The greatest IE risk is associated with the most complicated congenital malformations, such as operated pulmonary atresia with ventricular septal defect (VSD) and the tetralogy of Fallot. (Morris, Reller et al. 1998) A small hemodynamically insignificant VSD causes significant jet streams and endothelial damage and a high risk of IE. In about 10% of the male population, the aortic valve is bicuspid, which contributes to a somewhat increased likelihood of infection. However, the most common cardiovascular diagnosis encountered with IE today is mitral valve prolapse. (Mylonakis and Calderwood 2001) Only patients with valve regurgitation have an elevated risk. (Zuppiroli, Rinaldi et al. 1995) The incidence of IE in persons with known mitral valve prolapse is approximately 100 per 100 000 person years, and it may be even higher in males above the age of 45 years. (Bonow, Carabello et al. 1998)

Degenerative valve lesions are present in up to 50% of patients with IE who are older than 60 years. (McKinsey, Ratts et al. 1987) The incidence of such lesions is extremely high in hemodialysis patients and is one explanation why this patient population is prone to IE. (Straumann, Meyer et al. 1992) The risk of IE is constantly raised in patients who have a history of endocarditis. (Steckelberg and Wilson 1993) The proportion of patients with no previous valve deficit is, nevertheless, increasing. (Hoen, Alla et al. 2002)

Prosthetic valve endocarditis (PVE) accounts for 15-30% of all IE in most developed countries. (Cabell, Jollis et al. 2002; Hoen, Alla et al. 2002) The cumulative risk of PVE is approximately 1.4-3.1% at 12 months and 3.0-5.7% at 5 years. (Arvay and Lengyel 1988; de Gevigney, Pop et al. 1995; Mylonakis and Calderwood 2001) Progressive endothelialization of the prosthetic material over a few months reduces the susceptibility of the valve for infection. Mechanical prosthetic valves appear to be associated more strongly with endocarditis soon after surgery than bioprosthetic valves. Later on, however, the risk of IE in bioprosthetic valves surpasses that associated with mechanical protheses. (Calderwood, Swinski et al. 1985; Arvay and Lengyel 1988) Implantable rings (as part of valve repair) are associated with the lowest risk for endocarditis. (Gordon, Serkey et al. 2000) Endocarditis with an onset within 2 months after surgery is called early PVE. It is usually acquired in hospital, and is frequently caused by coagulase-negative staphylococci or *Staph. aureus*. (Piper, Korfer et al. 2001) Endocarditis that becomes manifest later than 12 months after surgery is called late PVE and is regarded as community-acquired. (Tornos, Almirante et al.

1997; Mylonakis and Calderwood 2001) Endocarditis that emerges 2-12 months after surgery constitutes a mixture of hospital-acquired endodarditis caused by less virulent organisms and community-acquired endocarditis. (Calderwood, Swinski et al. 1986)

Intracardiac devices (e.g. pacemakers and implantable cardioverter defibrillators) are an integral part of modern cardiovascular medicine. Recent evidence of the US Medicare population has shown that the rate of implantation of new devices rose by 42% in the 1990s but that there was a 124% relative increase in the proportion of patients with documented device infections during the same time period. (Cabell, Heidenreich et al. 2004) In fact, intracardiac devices carry an IE risk similar to prosthetic valves. (Gordon, Quagliarello et al. 2006)

In the developing countries, rheumatic valve disease, which occurs primarily in the young, is the most frequent predisposing factor for IE. (Jalal, Khan et al. 1998)

2.3.2. Dental

It is widely accepted that dental procedures are associated with a risk of IE in patients with a variety of cardiac diseases; the exceptions being dental procedures with no risk of gingival or mucosal trauma and subsequent bleeding. However, the relation of IE to dental procedures has been overemphasized in the past, and IE is now more likely in the context of previous valve surgery, or as a consequence of iatrogenic or nosocomial infection than dental procedures. (Bouza, Menasalvas et al. 2001) For example, Strom and colleagues did nor find any association between dental procedures and subsequent endocarditis in a population-based case-control study. (Strom, Abrutyn et al. 1998) In patients with poor oral hygiene even routine daily activities, like tooth-brushing or chewing can cause significant bacteremia. This probably explains why oral streptococci predominate, and why in most instances of IE the disease is not preceded by medicosurgical procedures. (van der Meer, Thompson et al. 1992; Strom, Abrutyn et al. 1998) Thus, even if antibiotic prophylaxis during dental procedures were effective, it would only prevent a limited number of cases. (Van der Meer, Van Wijk et al. 1992; Horstkotte, Follath et al. 2004)

2.3.3. Intravenous drug use

Currently, IVDU is one of the most common causes of IE in the developed countries. The incidence of endocarditis in IVDU patients is 150-2000 per 100 000 person years. (Manoff, Vlahov et al. 1996; Frontera and Gradon 2000) Up to 20% of hospital admissions, and 5-10% of total deaths among drug addicts is due to IE. In a large patient series from the Detroit Medical Center, 41% of drug addicts with bacteremia had IE. (Levine, Crane et al. 1986)

Most of these patients are young adult (20-35 years) males (male:female ratio 3:1). (Miro, del Rio et al. 2002) The tricuspid valve is affected in 60-70% of cases, followed by the aortic valve and the mitral valve each in 10-20%, and mixed right-sided and left-sided IE in 5-10% of cases. (Mathew, Addai et al. 1995; Miro, del Rio et al. 2002; Ruotsalainen, Sammalkorpi et al. 2006) Only 10-30% of the drug addicts have a pre-existing valve lesion. (Mathew, Addai et al. 1995; Miro, del Rio et al. 2003)

The pathogens usually originate from the drug addict's own skin, explaining the predominance of *Staph. aureus* (60-70%). (Mathew, Addai et al. 1995; Siddiq, Missri et al. 1996; Miro, del Rio et al. 2003) Drug addicts are in a habit of cleaning the needles for injection of the drug with saliva and this obvioulsy leads to IE caused by pathogens residing in the oral cavity, e.g. viridans streptococci. Enterococci, *Pseudomonas aeruginosa* and fungi are also common causes of IE among patients with IVDU. (Shekar, Rice et al. 1985) Endocarditis associated with IVDU is more often polymicrobial than in the general population. (Levine, Crane et al. 1986) HIV-positive patients sometimes present with IE caused by unusual organisms, including *Bartonella* spp., *Salmonella* spp., and *Listeria monocytogenes*. In these patients, both the risk and the mortality from IE rise in inverse relation to the CD4 count; the risk is not raised in patients with CD4 counts of more than 500 cells per µl, but increases 4-fold when the CD4 count is less than 200 cells per µl. (Wilson, Thomas et al. 2002) In conformity with this observation, the risk of IE among HIV-infected patients who do not abuse drugs is not increased.

2.3.4. Nosocomial

Nosocomial IE is defined as IE that arises later than 72 h after admission to hospital, or within 4 to 8 weeks of hospital-based invasive procedures. (Ben-Ami, Giladi et al. 2004; Haddad, Arabi et al. 2004) In some recent series, 7 to 29% of IE have a nosocomial origin (Berlin, Abrutyn et al. 1995; Fernandez-Guerrero, Verdejo et al. 1995; Bouza, Menasalvas et al. 2001), and probably less than half of these patients have some cardiac predisposing factor. (Bouza, Menasalvas et al. 2001) Sources of infection include surgical wounds, vascular catheters, arteriovenous fistulae used for hemodialysis, and genitourinary and gastrointestinal tract procedures. (Fernandez-Guerrero, Verdejo et al. 1995; Fowler, Miro et al. 2005)

Staphylococci and enterococci predominate as the nosocomial pathogens causing IE. (Bouza, Menasalvas et al. 2001; Hoen, Alla et al. 2002; Ben-Ami, Giladi et al. 2004; Haddad, Arabi et al. 2004) Especially *Staph. aureus* and *Staph. epidermidis* are able to form a biofilm, which impedes microbial clearance, and often mandates device removal for eradication of infection. (Cramton, Gerke et al. 1999) More than 50% of cases in hemodialysis patients are due to *Staph. aureus.* (Abbott and Agodoa 2002; Cabell, Jollis et al. 2002)

2.4. Microorganisms in IE

IE is more often due to Gram-positive than Gram-negative bacteria, possibly because these pathogens adhere differently to damaged valves, or because of differences in their susceptibility to serum-induced microbial killing. (Moreillon, Que et al. 2002) Together *Staph. aureus*, *Streptococcus* spp., and enterococci cause more than 80% of all instances of IE (**Table 2**).

Table 2. Microbiology of infective endocarditis (IE) in general population and in specific at-risk groups*

	Native valve IE (N =355)	IE in IVDU (N= 87)	Prosthetic valve IE	
			Early (N = 25)	Late (N = 90)
Pathogen				
Staphylococci	138 (39%)	60 (69%)	12 (48%)	37 (41%)
Staph. aureus	118 (33%)	60 (69%)	3 (12%)	17 (19%)
CoNS°	20 (6%)	0	9 (36%)	20 (22%)
Streptococci	120 (34%)	7 (8%)	2 (8%)	28 (31%)
Viridans streptococci	87 (25%)	3 (3%)	2 (8%)	22 (24%)
Others	33 (9%)	4 (5%)	0	6 (7%)
Enterococcus spp.	26 (7%)	2 (2%)	3 (12%)	10 (11%)
HACEK-group†	13 (4%)	0	0	1 (1%)
Polymicrobial	6 (2%)	8 (9%)	0	1 (1%)
Other bacteria	19 (5%)	4 (5%)	2 (8%)	5 (6%)
Fungi	3 (1%)	2 (2%)	1 (4%)	0
Negative blood culture	30 (8%)	4 (5%)	5 (20%)	8 (9%)

* Data from studies with comparable microbiological details (Watanakunakorn and Burkert 1993; Sandre and Shafran 1996; Bouza, Menasalvas et al. 2001; Fefer, Raveh et al. 2002)

° Coagulase-negative staphylococci

† Includes *Haemophilus spp., Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae*

In recent series, staphylococci, particularly *Staph. aureus*, have surpassed the viridans group of streptococci as the most common cause of IE, and staphylococci account for 30-40% of all cases of IE. (Hogevik, Olaison et al. 1995; Cabell, Jollis et al. 2002; Hoen, Alla et al. 2002; Mouly, Ruimy et al. 2002; Ruotsalainen, Sammalkorpi et al. 2006) This increase appears to be due, in large part, to increasing healthcare contacts of the general population. *Staph. aureus* is also the most common microbe among endocarditis associated with IVDU. (Ruotsalainen, Sammalkorpi et al. 2006) The prevalence of endocarditis among patients with *Staph. aureus* bacteremia is 10-30%. (Li, Sexton et al. 2000; Fowler, Olsen et al. 2003) The microbe may easily attack also healthy heart valves, and the course of the disease is frequently fulminant when it involves the mitral or aortic valve. Factors associated with an increased probability of IE in patients with *Staph. aureus* bacteremia include community acquisition, absence of a primary focus, metastatic sequelae, fever, and bacteremia persisting for more than 3 days after catheter removal.

In addition, coagulase-negative staphylococci, which are the most common pathogens in early PVE, have been well documented as occasionally causing native valve endocarditis (NVE). (Chu, Cabell et al. 2004) One species of coagulase-negative staphylococcus, *Staph. lugdunensis*, can affect apparently normal valves among community-dwellers, and it requires often valve replacement due to progressive destruction of the valve by the inflammatory process. (Patel, Piper et al. 2000)

Streptococci have been the most frequent cause of IE, and are still so as regards in community-acquired IE (excluding IVDU). (Kanafani, Mahfouz et al. 2002) The most common streptococci isolated from patients with endocarditis are still *Streptococcus sanguis*, *Strep. bovis*, *Strep. mutans* and *Strep. mitis*. They usually cause a subacute disease. *Strep. bovis* is prevalent among the elderly, and is often associated with pre-existing cancer of the gastrointestinal tract. (Hoen, Alla et al. 2002) *Strep. pneumoniae*

causes only some 3% of IE. (Bruyn, Thompson et al. 1990) The course of pneumococcal IE is often extremely fulminant. (Ugolini, Pacifico et al. 1986; Aronin, Mukherjee et al. 1998) Group B streptococci (*Strep. agalactiae*) are an important cause of invasive infections in neonates and adults. Risk factors for group B streptococcal sepsis and IE include diabetes mellitus, cancer, alcoholism, hepatic failure, elective abortion and IVDU. (Sambola, Miro et al. 2002) Underlying heart disease is common and the mortality rate is nearly 50%. Group A streptococci are a very rare cause of IE, but are associated with a high complication rate. (Baddour 1998)

Enterococci belong to the normal flora of the gastrointestinal tract and occasionally the anterior urethra. They are frequently implicated in nosocomial bacteremia and are responsible for 5 to 18% of IE. (Patterson, Sweeney et al. 1995) The presentation of enterococcal IE is usually subacute. However, enterococcal IE is much less common than enterococcal bacteremia; the frequency of IE is less than 10% among those who have documented enterococcal bacteremia. (Fernandez-Guerrero, Verdejo et al. 1995; Patterson, Sweeney et al. 1995)

IE due to gram-negative bacilli is uncommon. Drug addicts, prosthetic valve recipients, and patients with liver cirrhosis appear to be at an increased risk. Among the *Enterobacteriaceae*, *Salmonella* spp. are important causes of endocarditis and aortitis. (Fernandez Guerrero, Aguado et al. 2004) Most (95%) of the patients with pseudomonas endocarditis are intravenous drug abusers, and eradication of pseudomonas from the heart valves is difficult. (Komshian, Tablan et al. 1990)

Blood cultures are negative in 10-14% of cases of endocarditis, and this often delays the diagnosis and start of the treatment. (Hoen, Selton-Suty et al. 1995; Lamas and Eykyn 2003) The most common cause of culture-negative disease is antibiotic use within the previous 2 weeks. According to some reports, only 5 to 7% of patients who have a diagnosis of IE according to strict criteria and who have not recently received antibiotics will have sterile blood cultures. (Hoen, Alla et al. 2002; Lamas and Eykyn 2003) Blood cultures can remain negative also when some fastidious organisms, for example the HACEK-group of microorganisms (*Hemophilus aphrophilus*, *H. paraphrophilus*, *H. parainfluenzae*, *H. influenzae*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*), or fungi, such as *Candida* and *Aspergillus* spp. are etiologically involved. Microorganisms of the HACEK-group require 2-3 weeks for primary isolation.

The predisposing factors for fungal IE include long-term antibiotic therapy, total parenteral nutrition through central vascular catheters, immunosuppressive therapy, reconstructive cardiovascular surgery, and IVDU. (Pierrotti and Baddour 2002; Martin, Mannino et al. 2003) Recent series of patients with endocarditis have implicated *Coxiella burnetii* (the cause of Q-fever), *Bartonella* spp., *Chlamydia* spp., *Legionella* spp., and *Mycoplasma* spp. as the cause in up to 24% of patients with blood culture-negative IE in some parts of the world. (Hoen, Selton-Suty et al. 1995; Lamas and Eykyn 2003)

2.5. Location of IE

Usually (90%) IE is situated on the left (high-pressure) side of the heart. The aortic and the mitral valve are almost equally affected (35-50% of cases). (Netzer, Zollinger et al. 2000; Hoen, Alla et al. 2002; Mouly, Ruimy et al. 2002) However, among patients with IVDU, tricuspid valve IE is the most common. (Mathew, Addai et al. 1995; Hoen, Alla et al. 2002) In 15-20% of all episodes, more than one valve is infected. (Mouly, Ruimy et al. 2002; Hasbun, Vikram et al. 2003) Rarely, IE is found on the pulmonic valve (1.5-2%), or in extravalvular locations, such as the atrial septum, ventricular wall, chordae tendinae or on mural endocardium. (Hasbun, Vikram et al. 2003; Hamza, Ortiz et al. 2004) The nature of the underlying valvular disease is important for the location of IE. Mitral IE is more common in rheumatic valvular affection, common among females, and aortic disease more prevalent in the atherosclerotic risk group, often males. In PVE, the aortic valve is involved most frequently. (Arvay and Lengyel 1988; Loupa, Mavroidi et al. 2004)

2.6. Symptoms and signs of IE

Fever is the most common symptom and sign of IE, and occurs in up to 90% of all patients with IE; often the fever is associated with chills. (Tornos 2005) However, fever may be absent or minimal in immunocompromized patients, in patients who have previously used antimicrobial drugs, and if the IE is caused by less virulent organisms. Heart murmurs (which usually have pre-existed) are heard in up to 85% of patients. However, *Staph. aureus* IE is usually associated with no murmur at all when the patient is admitted. (Hogevik, Olaison et al. 1995) Tachycardia may be the first clue to a low ejection fraction and incipient heart failure, before overt dyspnea develops. IE should always be considered in patients who present with heart failure and have no history of antecedent cardiac disease, especially if any of the classic findings are present (e.g. fever, murmur, vascular phenomena).

Common symptoms of subacute IE include anorexia, weight loss, malaise, fatigue, arthralgias, myalgias and night sweats. Patients may have splenomegaly, vascular phenomena, like splinter hemorrhages under the fingernails or toenails, petechiae on the skin, conjunctivae, or oral mucosa, and Janeway's lesions. Immunological phenomena, e.g. membranoproliferative glomerulonephritis (GN), positive rheumatoid farctor, Osler's nodes and Roth's spots may also be found. In almost 40% of patients with IE, embolism is obvious at the time of diagnosis. (Hogevik, Olaison et al. 1995) The "blue toe syndrome" is caused by embolization of small vegetation fragments, which cause ischemia in the distal extremities.

Acute IE usually involves the left-sided heart valves (except in patients with IVDU), and evolves rapidly and dramatically: the patient has severe sepsis and rapidly progressive cardiac failure. Many of these patients have no pre-existing heart disease. Usually, these infections are due to virulent pathogens, such as *Staph. aureus* and *Strep. pneumoniae*. The onset of nosocomial IE is also often acute, and the classical signs of IE are infrequent. (Gouello, Asfar et al. 2000) PVE may manifest as an indolent illness with low-grade fever, or it can be an acute febrile and toxic illness.

Unexplained fever or valvular dysfunction in a patient with a prosthetic valve should prompt careful evaluation for PVE.

In a Swedish epidemiological study, the median duration of IE-related symptoms was 14 days. (Hogevik, Olaison et al. 1995) When the IE was caused by *Staph. aureus*, duration was shorter (only 6 days) than when it was caused by viridans streptococci (27 days). The pretreatment duration is important not only for outcome, but also for the clinical presentation. Weight loss and splenomegaly are currently rare findings, as intervention usually starts earlier than in the preceding decades.

IE associated with IVDU is often an acute febrile syndrome. On admission, the murmur of tricuspid insufficiency is usually absent but appears later in about half of the patients. Pulmonary embolism, often misdiagnosed as pneumonia is frequent in right-sided IE and presents with cough, pleuritic pain, hemoptysis and dyspnea. (Miro, del Rio et al. 2003) Right-sided endocarditis should therefore always be suspected in drug addicts with fever and radiological pulmonary infiltrates despite the absence of significant heart murmurs. The clinical features of left-sided IE in patients with IVDU do not differ from those in a non-drug addict population. (Mathew, Addai et al. 1995) *Staph. aureus* is the most common causative agent, and the disease often manifests with septic metastases.

2.7. Diagnosis of IE

The single most important diagnostic factor regarding IE is a clinical suspicion. The possibility of IE should be considered in any patient who has unexplained fever with a duration of more than one week, especially if that patient has a known predisposition to IE. The presenting features are all too often far from classic.

2.7.1. Classification

Due to the highly variable clinical manifestations of endocarditis, different sets of diagnostic criteria have been used to direct and standardize case definitions in clinical practice and in scientific work. The first distinct case definition of IE was proposed by Pelletier and Petersdorf in 1977. (Pelletier and Petersdorf 1977) A few years later, von Reyn et al. (Von Reyn, Levy et al. 1981) presented a modification, which aimed at improving the sensitivity and specificity of these diagnostic criteria (**Table 3**). According to the von Reyn classification, histopathologic evidence is necessary for a diagnosis of definite IE, while a likelihood of IE is based on blood culture findings, on the presence of fever, on various heart conditions that predispose to or indicate IE, and on the presence of vascular manifestations.

In 1994, Durack at the Duke University introduced a new classification system. (Durack, Lukes et al. 1994) The main new elements were the inclusion of certain echocardiographic findings and a history of predisposing IVDU (**Tables 3** and **4**). According to the Duke classification, a case can be designated as definite IE based on clinical and echocardiographic findings alone. The usefulness of the Duke criteria for assessing patients with potential IE has been validated in several studies. (Bayer, Ward et al. 1994; Olaison and Hogevik 1996; Sekeres, Abrutyn et al. 1997; Perez-Vazquez, Farinas et al. 2000)

Table 3. Definitions of infective endocarditis according to the criteria of von Reyn et al.* and Duke°

von Reyn criteria	**Duke criteria**
Definite • Direct evidence of infective endocarditis based on histologic examination from surgery or autopsy, or • Bacteriologic testing (Gram stain or culture) of valvular vegetation or peripheral embolus	**Definite** **Pathologic criteria**: • Microorganisms: demonstrated in a vegetation or In a vegetation that has embolized, or in an intracardiac abscess by ° culture or ° histologic examination • Pathologic lesions: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis **Clinical criteria**, using specific definitions listed in Table 4 • 2 major criteria, or • 1 major and 3 minor criteria, or • 5 minor criteria
Probable • Persistently positive blood cultures∂ plus 1 of the following: ° New regurgitant murmur, or ° Predisposing heart disease† and vascular phenomena‡ • Negative or intermittently positive blood cultures§ plus all 3 of the following: ° Fever ° New regurgitant murmur ° Vascular phenomena	
Possible • Persistently positive blood cultures plus 1 of the following: ° Predisposing heart disease ° Vascular phenomena • Negative or intermittently positive blood cultures plus all 3 of the following: ° Fever ° Predisposing heart disease ° Vascular phenomena • For viridans streptococcal cases only: ° 2 or more positive blood cultures without an extracardiac source, and fever	**Possible** • Findings consistent with infective endocarditis that fall short of "Definite", but are not rejected
Rejected • Endocarditis unlikely, alternate diagnosis generally apparent • Endocarditis likely, empiric antibiotic therapy warranted • Culture-negative endocarditis diagnosed clinically, but excluded by postmortem examination	**Rejected** • Firm other diagnosis for manifestations of endocarditis, or • Resolution of manifestations of endocarditis, with antibiotic therapy for 4 days or less, or • No pathologic evidence of infective endocarditis at surgery or autopsy, after antibiotic therapy for 4 days or less

* According to von Reyn, Levy et et al. 1981

° According to Durack, Lukes et al.1994

∂ At least 2 blood cultures obtained, with 2 of 2 positive, 3 of 3 positive, or at least 70% of cultures positive if 4 or more cultures obtained

† Definite valvular or congenital heart disease, or a cardiac prosthesis (excluding permanent pacemakers)

‡ Petechiae, splinter hemorrhages, conjunctival hemorrhages, Roth spots, Osler's nodes, Janeway lesions, aseptic meningitis, glomerulonephritis, and pulmonary, central nervous system, coronary or peripheral emboli

§ Any rate of blood culture positivity that does not meet the definition of persistently positive

Despite the high sensitivity and specificity of the original Duke criteria, they have subsequently been modified to include the role of Q-fever, the application of the PCR method in the microbiological diagnosis of IE, and the increasing prevalence of *Staph.*

aureus as the causative agent of IE. (Li, Sexton et al. 2000) According to the modified Duke criteria, the definition "minor echocardiographic finding" is omitted because of the widespread adoption of transesophageal echocardiography (TEE). In addition, Lamas and Eykyn have suggested that recent digital clubbing, splenomegaly, high erythrocyte sedimentation rate (ESR), high serum CRP, hematuria, and venous lines should be considered as minor criteria. (Lamas and Eykyn 1997)

Table 4. Terminology of the Duke criteria*

Major criteria
Positive blood culture for infective endocarditis
• Typical microorganism for infective endocarditis from 2 separate blood cultures ° Viridans streptococci†°, *Streptococcus bovis*, HACEK‡ group, or ° community-acquired *Staphylococcus aureus* or enterococci, in the absence of a primary focus, or
• Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from: ° Blood cultures drawn more than 12 hours apart, or ° all of 3 or a majority of 4 or more separate blood cultures with first and last drawn at least 1 hour apart
Evidence of endocardial involvement
• Positive echocardiogram for infective endocarditis ° Oscillating intracardiac mass, on valve or supporting structures, or in the path of regurgitant jets, or on implanted material, in the absence of an alternative anatomic explanation, or ° Abscess, or ° New partial dehiscence of prosthetic valve, or
• New valvular regurgitation (increase or change in pre-existing murmur not sufficient)
Minor criteria
Predisposition
• Predisposing cardiac condition
• Intravenous drug use
Fever ≥38.0°C (100.4°F)
Vascular phenomena
• Major arterial emboli
• Septic pulmonary infarcts
• Mycotic aneurysm
• Intracranial haemorrhage
• Conjunctival haemorrhages
• Janeway lesions
Immunologic phenomena
• Glomerulonephritis
• Osler's nodes
• Roth spots
• Rheumatoid factor
Microbiologic evidence
• Positive blood culture but not meeting major criterion as noted previously§ or
• Serologic evidence of active infection with organism consistent with infective endocarditis
Echocardiogram
• Consistent with infective endocarditis but not meeting major criterion as noted previously

* According to Durack, Lukes et al. 1994

† Including nutritional variant strains

‡ HACEK is *Haemophilus* spp., *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* spp., and *Kingella kingae*

§ Excluding single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis

Since the diagnosis of IE is difficult, the patients are often admitted under other diagnoses than IE. According to Hogevik et al. (Hogevik, Olaison et al. 1995), only 36% of their patients with IE had IE as the initial primary diagnosis. In episodes caused by *Staph. aureus*, a correct admission diagnosis of IE was made only in 17%.

2.7.2. Blood cultures

Blood culture is the best identification method and provides live bacteria for susceptibility testing. Currently, 3 sets of blood of 5-10 ml, each drawn one hour apart (over 24-48 h) incubated in both aerobic and anaerobic atmospheres, are regarded as standard. (Houpikian and Raoult 2002; Horstkotte, Follath et al. 2004) For the main causative agents, the first 2 blood cultures will be positive in more than 90% of cases. No evidence suggests that cultures should be taken coincident with peaks of temperature, since bacteremia is constant. However, cultures should not be taken from indwelling lines because of the high likelihood of contamination.

Ideally, one should wait at least 24 hours after the previous dose of antibiotic before collecting blood cultures to ensure detection of bacterial growth. Discontinuation of antibiotic therapy that has been initated is not recommended if there is evidence of IE. Identification of a pathogen in culture-negative disease depends on special procedures, e.g. by inactivation antibiotics in the culture media, prolonged incubation (≥2 weeks), serology, agglutination, indirect fluorescence, ELISA and complement fixation, and PCR. (Brouqui and Raoult 2001; Houpikian and Raoult 2002)

2.7.3. Molecular diagnosis

PCR amplification of 16S ribosomal RNA gene, i.e., genes that are specific for bacteria, has provided excellent results when used on surgically resected material or systemic emboli of patients with IE. (Goldenberger, Kunzli et al. 1997; Houpikian and Raoult 2002) The PCR approach has been useful especially in blood culture-negative IE, and in IE caused by fastidious or non-culturable microbes, especially *Bartonella* spp., *C. burnetii*, and *Tropheryma whipplei*. (Raoult, Fournier et al. 1996; Goldenberger, Kunzli et al. 1997; Gubler, Kuster et al. 1999; Brouqui and Raoult 2001; Lisby, Gutschik et al. 2002)

Gauduchon and colleagues estimated that PCR of valve tissue changed the diagnosis and management in 20% of patients of IE. (Gauduchon, Chalabreysse et al. 2003) Limitations of the PCR method include the potential for contamination and the limited number and quality of DNA sequences currently available. (Lepidi, Durack et al. 2002)

2.7.4. Serology

Serological testing is particularly useful for investigating the possibility of microbes that cannot be cultured by routine methods. (Li, Sexton et al. 2000; Brouqui and Raoult 2001; Lamas and Eykyn 2003) If previous antimicrobial treatment has not been administered and blood cultures are negative, fastidious organisms should be suspected and the titers of antibodies against *C. burnetii, Bartonella* spp., *Mycoplasma pneumoniae*, *Chlamydia* spp., *Legionella pneumophila*, and *Brucella* spp. should be systematically determined. (Houpikian and Raoult 2002)

2.7.5. Histology

Histological examination of the excised valve can confirm the diagnosis by demonstrating tissue changes compatible with IE. It may also detect organisms that fail to grow in culture, especially in patients who have received previous antmicrobial medication. (Lepidi, Durack et al. 2002) Tissue cell culture is necessary for culturing obligate intracellular organisms, such as *C. burnetii*, *T. whipplei*, and *Chlamydia psittaci*. (Houpikian and Raoult 2002) Culturing of the excised valve material can facilitate the etiological diagnosis since it often harbors large amounts of bacteria. (Brouqui and Raoult 2001) Fungal IE can also be diagnosed by histopathology. (Werner, Andersson et al. 2003)

2.7.6. Echocardiography

The characteristic echocardiographic finding is a vegetation on a valvular cusp, but often an increase in valvular leakage is the only sign of IE. In PVE, paravalvular leakage and dehiscence of the prosthetic valve are often recorded. Extravalvular extension of the infection with abscess formation should be diagnosed early, as this condition usually indicates surgery. IE cannot always be excluded by a normal echocardiography, since endocardial infection may be erosive and superficial, or the vegetation may have embolized.

Transthoracic echocardiography (TTE) is rapid and non-invasive and is therefore often the intial technique for investigating IE. However, it may be inadequate in up to 20% of adult patients because of obesity, chronic obstructive pulmonary disease, chest-wall deformities, or previous valvular deformities. Actually, the overall sensitivity for detection of vegetations may be no more than 60-80%. (San Roman, Vilacosta et al. 1993; Werner, Schulz et al. 1996; Reynolds, Jagen et al. 2003; Jassal, Aminbakhsh et al. 2007) Conversely, TTE detects tricuspid vegetations with a reported sensitivity as high as 80%, a sensitivity almost similar to that of TEE. (Bayer, Blomquist et al. 1988)

TEE causes more discomfort to the patient than TTE but increases the sensitivity for detecting vegetations to 75-95% with a specificity of 85-98% (**Table 5**). (Mugge, Daniel et al. 1989; Shively, Gurule et al. 1991; Shapiro, Young et al. 1994; Werner, Schulz et al. 1996) TEE is more sensitive than TTE for defining perivalvular extension of infection and the presence of myocardial abscess, and it is particularly useful in patients with prosthetic valves. (Daniel, Mugge et al. 1993; Choussat, Thomas et al. 1999; Horstkotte, Follath et al. 2004) TEE with color-flow Doppler techniques can also demonstrate the distinctive flow patterns of fistulas, pseudoaneurysms, or unruptured abscess cavities, and it is more sensitive for identifying valve perforations. (De Castro, Cartoni et al. 2000) A strategy of initial TEE imaging might be most cost-effective in most situations. (Heidenreich, Masoudi et al. 1999; Rosen, Fowler et al. 1999)

2.7.7. Electrocardiography

The main clinical impact of the electrocardiogram (ECG) in the management of IE is that conduction abnormalities often precede TEE evidence of perivalvular extension of infection. New atrioventricular, fascicular, or bundle-branch block, particularly in the setting of aortic valve endocarditis, suggests perivalvular invasion, and indicates a need

for careful cardiac monitoring. (DiNubile, Calderwood et al. 1986; Daniel, Mugge et al. 1991)

Table 5. Detection of echocardiographic findings associated with infective endocarditis (IE) with transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE)

First author, Year	No. of patients	Classification	Echocardiographic finding	Detected by TTE (%)	Detected by TEE (%)
Mugge, 1989	105	Active IE	Vegetation	58	90
Daniel, 1991	44	IE with perivalvular abscess*	Perivalvular abscess	28	87
Shively, 1991	62	Suspected IE	Vegetation	44	94
Birmingham, 1992	61	Suspected IE	Vegetation	30	88
San Roman, 1993	48	Suspected right-sided IE	Right-sided vegetation	44	44
Shapiro, 1993	64	Suspected IE	Vegetation	68	97
Werner, 1996	106	Definite IE	Vegetation	58	92
Choussat, 1999	233	IE with perivalvular abscess*	Perivalvular abscess	36	80
Reynolds, 2003	50	IE confirmed by TEE	Vegetation	55	100°
Jassal, 2007	36	IE confirmed by TEE	Vegetation	84	100°

* Confirmed by surgery or autopsy

° Included only patients with vegetations detected by TEE

2.7.8. Other imaging modalities

Chest radiography can be used to provide supporting evidence of IE, such as nodular pulmonary infiltrates signifying right-sided IE with septic pulmonary emboli. In addition, cardiomegaly may indicate chamber enlargement due to significant valvular regurgitation, while enlarged pulmonary vessels provide evidence of congestive heart failure (CHF).

Computed tomography (CT) and magnetic resonance imaging (MRI) have been used to assess for evidence of thromboembolic complications, such as stroke or visceral embolic events, in patients with IE, but their role in imaging cardiac pathology is less well established. Indium-tagged white cells scans may also be helpful in detecting abscesses at various body sites.

2.7.9. Laboratory tests

Blood analyses other than blood cultures are unspecific for IE. Determination of serum CRP is useful, while ESR is normal in 33% of patients on admission. (Hogevik, Olaison et al. 1997) The CRP concentration at the time of diagnosis is often moderate, the median concentration being 90 mg/l for all etiologies of IE, and is about 50 mg/l for viridans streptococcal and 150 mg/ml for *Staph. aureus* IE. (Hogevik, Olaison et al. 1997) Anemia and leukocytosis are common. Microscopic hematuria is present in about half of the patients and is more common with *Staph. aureus* than viridans streptococci. (Watanakunakorn and Burkert 1993; Sandre and Shafran 1996)

2.8. Complications of IE

2.8.1. Cardiac complications

Over 50% of patients with IE sustain a serious complication. (Fefer, Raveh et al. 2002; Hoen, Alla et al. 2002; Mouly, Ruimy et al. 2002) CHF is the most common life-threatening complication, especially in aortic valve IE, and the principal cause of death

of IE patients. (Mylonakis and Calderwood 2001) It is usually caused by infection-induced valvular damage and not by myocardial failure. Endocarditis vegetations on native valves may mechanically interfere with valve motion and result in valvular regurgitation. Vegetation growth often results in leaflet perforation and may cause chordal rupture. Further cardiac complications include various kinds of fistulas, pericarditis, hemopericardium and tamponade. Extension outside the valve leaflets may cause perivalvular or myocardial abscesses leading to conduction disturbances. Rarely, embolism of fragments of vegetations can cause acute myocardial infarction and subsequent CHF.

Endocarditis on prosthetic valves begins usually on the valvular cuff and often extends outside the valvular apparatus, resulting in valvular dehiscence, abscess formation and myocardial involvement. In bioprosthetic valves, the valvular tissue itself is often involved, as well. Peri-annular extension and abscess formation are more frequent in PVE (56-100%) than in NVE (10-40%). (Choussat, Thomas et al. 1999) Extension of IE beyond the valve annulus predicts higher mortality, a more frequent development of CHF, and a need for cardiac surgery.

2.8.2. Neurological complications

The second most frequent complication is embolization. (Di Salvo, Habib et al. 2001) Mitral IE is associated with a somewhat higher risk of embolic events than aortic IE, and these events are also more prevalent in *Staph. aureus* IE than in episodes caused by viridans streptococci. (Cabell, Pond et al. 2001; Anderson, Goldstein et al. 2003) Detection of vegetations $\geq$10 mm or mobile vegetations correlates to an increased risk of embolization. (Cabell, Pond et al. 2001; Di Salvo, Habib et al. 2001; Wallace, Walton et al. 2002; Granowitz and Longworth 2003; Deprele, Berthelot et al. 2004; Thuny, Di Salvo et al. 2005) The rate of embolic events in patients with IE decreases rapidly after the initiation of effective antibiotic therapy. (Steckelberg, Murphy et al. 1991; Chu, Cabell et al. 2004; Deprele, Berthelot et al. 2004)

Up to 65% of IE-related embolic events involve the central nervous system (CNS) and they are prognostically the most important. Neurological complications develop in 14-40% of all patients with IE and they are often the presenting sign (**Table 6**). (Jones and Siekert 1989; Valtonen, Kuikka et al. 1993; Millaire, Leroy et al. 1997; Roder, Wandall et al. 1997) They consist of embolic stroke, transient ischemic attack (TIA), brain hemorrhage, meningitis, toxic encephalopathy and brain abscess, of which stroke is the most common. (Fefer, Raveh et al. 2002; Hoen, Alla et al. 2002; Mouly, Ruimy et al. 2002) Mycotic aneurysms may be responsible for up to 15% of neurological manifestations. They result from septic embolization of vegetation to the arterial vasa vasorum or the intraluminal space, with consequent spread of infection through the intima and vessel wall. Mycotic aneurysms in the cerebral circulation may bleed into the cerebral ventricles, and neurosurgical intervention is usually required. The clinical syndrome that results from aneurysmal hemorrhage may vary considerably from a slow leak that produces only mild headache and meningeal irritation to sudden intracranial hemorrhage and death. (Mylonakis and Calderwood 2001) Imaging procedures (CT, MRI, MR angiography) to detect intracranial mycotic aneurysms may be useful in patients with localized or severe headaches, meningitis with negative cultures, or focal

neurological signs. (Bayer, Bolger et al. 1998) Angiography should be performed when a patient presents with subarachnoid hemorrhage to establish the presence and localization of any aneurysms (**Figure 1**).

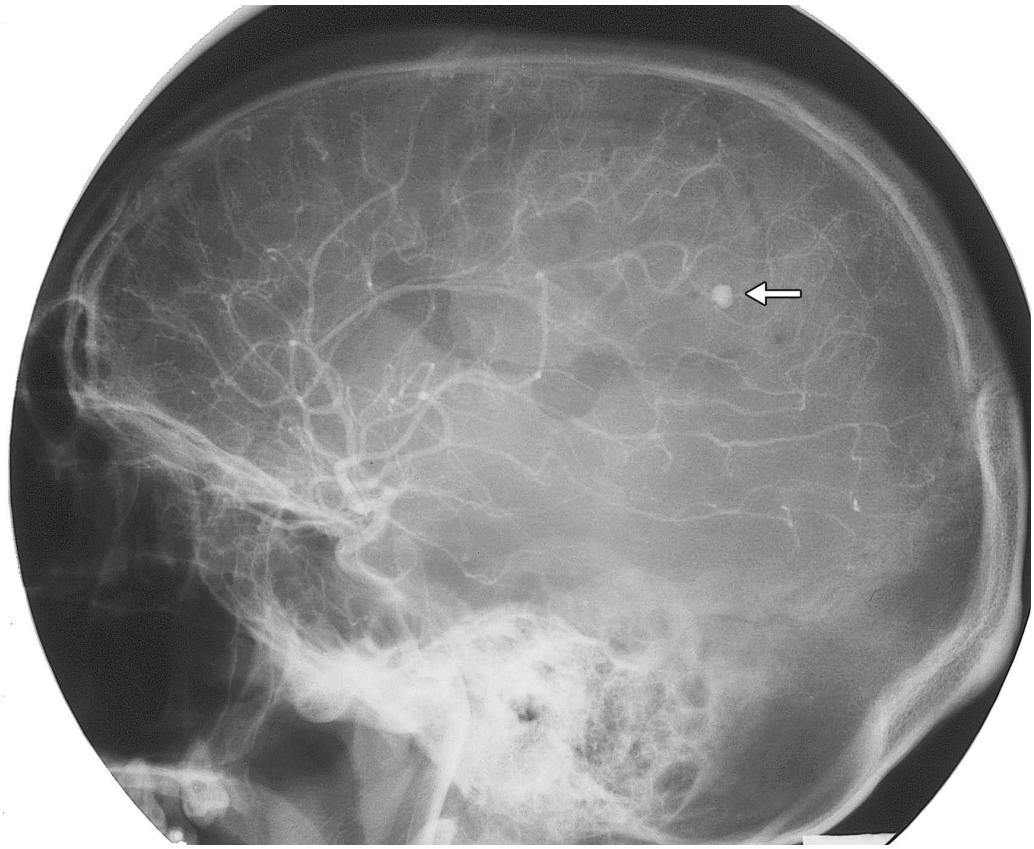

Figure 1. Carotid angiography demonstrates a mycotic aneurysm (arrow) of the peripheral branches of the middle cerebral artery

2.8.3. Peripheral emboli

Systemic embolism usually involves the spleen, the kidneys, the liver, and iliac or mesenteric arteries. Other common sites of emboli are the skin, joints and the skeleton. (Fefer, Raveh et al. 2002; Hoen, Alla et al. 2002; Mouly, Ruimy et al. 2002; Cecchi, Forno et al. 2004) Right-sided IE frequently causes pulmonary embolization that occurs in 40-75% of drug addicts who have tricuspid valve endocarditis. (Mathew, Addai et al. 1995; Ruotsalainen, Sammalkorpi et al. 2006)

Splenic abscess may cause prolonged fever and diaphragmatic irritation with pleuritic or left shoulder pain; abdominal pain and splenomegaly may be absent. (Bayer, Bolger et al. 1998)

Table 6. Neurological complications associated with infective endocarditis (IE) reported since the 1960's

First author, year	No. of IE episodes	No. of neurological complications (%)	Incidence in aortic/ mitral / aortic + mitral/ tricuspid valve IE (%)	Incidence in IE caused by *Staph. aureus*/ streptococci/ other microbes (%)	Ischemic stroke (%)	Brain hemorrhage (%)	In-hospital mortality in episodes with neurological complications (%)
Jones, 1969	385*	110 (29)	NG°	NG°	44 (11)	11 (3)	55 (50)
Pruitt, 1978	218*	84 (39)	25/50/12/34	53/30/45	38 (17)	15 (7)	49 (58)
Salgado, 1989	175§	64 (37)	35/38¶	65/36/30	30 (17)	3 (2)	13 (21)
Davenport, 1990	62†	17 (28)	30/24‡	33/11/34	11 (18)	6 (8)	10 (59)
Kanter, 1991	166*	58 (35)	36/42/54/12	67/25/50∂	33 (20)	8 (5)	NG°
Millaire, 1997	68°	23 (34)	NG°	NG°	18 (26)	1 (1)	NG°
Andersson, 2003	707*	101 (14)	9/17/NG°/NG°	NG°	49 (7)	17 (2)	24 (35)

* All with native valve IE (NVE)
° Not given
§ 113 with NVE, 62 with prosthetic valve IE (PVE)
¶ Incidence in NVE/PVE
† All with PVE
‡ Incidence in mechanical/bioprostheses
∂ Incidence in mitral and aortic valve IE only

2.8.4. Renal complications

Renal complications may occur in any form of endocarditis but are particularly frequent in patients with IE due to *Staph. aureus,* in up to 40-50% of cases. (Watanakunakorn and Burkert 1993; Sandre and Shafran 1996) Hematuria, proteinuria and an increased concentration of creatinine in the serum are signs of renal involvement. While most often attributed to immune complex GN, a recent necropsy and biopsy study of 62 patients with IE revealed that localized infarction was present in 31% and acute GN in 26%. (Majumdar, Chowdhary et al. 2000) Of the renal infarcts, over half were due to septic emboli, mostly in patients with *Staph. aureus* IE. Acute interstitial nephritis was found in 10%, but was largely attributable to antibiotic usage. Renal cortical necrosis was present in 10%. Azotemia due to immune complex GN generally improves with effective antibiotic therapy. The cause of renal failure is often multifactorial, especially, when there is impaired baseline renal function together with impaired hemodynamics and nephrotoxic drugs.

2.8.5. Prolonged fever

Fever associated with IE often resolves within 2 to 5 days after the start of appropriate antimicrobial treatment in patients with less virulent pathogens, and improvement occurs in 90% of patients by the end of the second week of treatment. The most common causes of persistent fever (more than 14 days) are extension of the infection beyond the valve, focal metastatic abscess, drug hypersensitivity (particularly if the fever resolves and then recurs), hospital-acquired infection other than IE or other complication of hospitalization, such as pulmonary embolism. (Blumberg, Robbins et al. 1992; Blumberg, Karalis et al. 1995) Up to 33% of patients may develop delayed adverse reaction from β-lactams necessitating drug withdrawal. (Olaison, Belin et al. 1999) Serial measurements of serum CRP concentrations are useful to monitor the

response to antimicrobial treatment and to detect complications, while serial ESR measurements are of no value in these situations. (Olaison, Hogevik et al. 1997)

2.9. Treatment of IE

2.9.1. General approach

Treatment of IE needs to be multidisciplinary and involve often specialists in infectious diseases, cardiology and cardiac surgery. A carefully documented initial physical examination, particularly focusing on the cardiopulmonary, cutaneous, and neurological systems, is important to insure that any new embolic phenomena will be noted, should they occur. Patients should undergo a cardiac examination daily and repeat echocardiography at any sign of IE complications. ECG should be taken weekly, especially if the patient has aortic valve endocarditis.

Prolonged fever or recurrence of fever needs careful evaluation. Patients should have surveillance blood cultures obtained to ensure that antimicrobial therapy is effective – these are usually obtained after 3 to 4 days of antimicrobial therapy. Any signs of hemodynamic instability or CHF should alert surgical consultation.

2.9.2. Antimicrobial therapy

The choice of the optimum regimen is based on antibiotic susceptibility testing. Minimum inhibitory concentrations (MIC) of the principal drug for the infecting pathogens should be ascertained. Prolonged (4-6 weeks) parenteral administration of bactericidal antibiotics is the cornerstone of therapy. (Wilson, Karchmer et al. 1995; Bayer, Bolger et al. 1998; Horstkotte, Follath et al. 2004; Baddour, Wilson et al. 2005; Thuny, Di Salvo et al. 2005) High concentrations of antibiotics in the serum are desirable to ensure diffusion into the vegetations. The recent recommendations for the antimicrobial treatment of IE have been issued by the European Society of Cardiology (Horstkotte, Follath et al. 2004) and the American Heart Association. (Baddour, Wilson et al. 2005; Bonow, Carabello et al. 2006). In **Tables 7-9**, the principles of these guidelines for the treatment of streptococcal, enterococcal, and staphylococcal endocarditis are presented.

Although most streptococci are sensitive to penicillin and other β-lactams, the proportion of resistant strains is increasing. Penicillin-resistant streptococci are classified as having either intermediate (MIC 0.1-0.5 mg/l) or high resistance (MIC >0.5 mg/l). Intermediately resistant streptococci might respond to standard penicillin therapy because the β-lactam concentration in the serum is much greater than the MIC for these bacteria. Nonetheless, potentiating the activity of β-lactams by combining them with an aminoglycoside (AG) is recommended in such situations (**Table 7**). Alternative drugs should be considered against highly resistant streptococci, e.g., vancomycin, to which streptococci are still widely susceptible. New fluoroquinolones (e.g. levofloxacin, moxifloxacine) may also be useful. (Entenza, Caldelari et al. 1999)

T**able 7**. Antimicrobial treatment for penicillin-susceptible (MIC <0.1 mg/l) or penicillin relatively resistant (0.1< MIC ≤0.5 mg/l) streptococcal infective endocarditis (IE)*

	No allergy to penicillin Drug	**Allergy to penicillin Drug**	**Duration**
Penicillin-susceptible streptococci (MIC <0.1 mg/l)			
Native valve IE	Penicillin G ± gentamicin or ceftriaxone ± gentamicin	Vancomycin	4 weeks β-lactam or vancomycin 2 weeks amino glycoside
Prosthetic valve IE	Penicillin G ± gentamicin or ceftriaxone ± gentamicin	Vancomycin	6 weeks β-lactam or vancomycin 2 weeks amino glycoside
Penicillin-relatively resistant streptococci G (0.1< MIC <0.5 mg/l)			
Native valve IE	Penicillin G + gentamicin or ceftriaxone + gentamicin	Vancomycin	4 weeks β-lactam or vancomycin 2 weeks amino glycoside
Prosthetic valve IE	Penicillin G + gentamicin or ceftriaxone + gentamicin	Vancomycin	6 weeks β-lactam or vancomycin 2 weeks amino glycoside

* Modified from Horstkotte, Follath et al. 2004 and Baddour, Wilson et al. 2005

Enterococci are rather resistant to penicillins. The optimal therapy for enterococcal IE requires a synergistic bactericidal combination of a cell-wall-active antimicrobial agent to which the organism is susceptible (ampicillin or vancomycin), plus an AG (**Table 8**). Multidrug-resistant enterococci are resistant to most drugs, including vancomycin. (Martone 1998) Treatment of such bacteria relies on the combination of multiple drugs and the use of experimental antibiotics. (Hoen 2006)

The most common antimicrobial agents used to treat staphylococcal IE include semisynthetic, penicillinase-resistant penicillins, cephalosporins, rifampicin and vancomycin. The cornerstone of the treatment of *Staph. aureus* IE is oxacillin or cloxacillin in combination with an AG for the first 3-5 days (**Table 9**). Vancomycin is less rapidly bactericidal against staphylococci than staphylococcal penicillins and the first-generation cephalosporins. (Levine, Fromm et al. 1991) All methicillin-resistant staphylococci carry a low-affinity penicillin-binding protein, which confers cross-resistance to all β-lactam antibiotics, regardless of the results of in vitro antimicrobial-susceptibility testing. Furthermore, methicillin-resistant staphylococci are resistant to many other antimicrobial agents, leaving mainly vancomycin or teicoplanin with which to treat severe infection. *Staph. aureus* and coagulase-negative staphylococci that are intermediately resistant to vancomycin have also emerged worldwide. (Hiramatsu, Aritaka et al. 1997) The mechanism of intermediate resistance is mediated by chromosomal mutations, which affect cell wall synthesis. (Geisel, Schmitz et al. 2001; Hiramatsu 2001) Moreover, a few highly vancomycin-resistant *Staph. aureus* organisms have been isolated clinically. Limited evidence suggests that linezolid may be considered as a therapeutic option for the treatment of patients with IE due to multidrug-resistant gram-positive cocci, including methicillin-resistant *Staph. aureus*. (Falagas, Manta et al. 2006)

AGs have, despite their potential toxicity, an established role in the treatment of IE. They have a good distribution into the vegetations and exert rapid bactericidal effects and, combined with a penicillin, act synergistically against most viridans streptococci and enterococci. (Wilson, Karchmer et al. 1995) AG may hinder the appearance of resistant strains during combined treatment regimens in PVE caused by coagulase-negative staphylococci. The use of one dose per day of AGs, commonly used to treat sepsis, is not yet standard in IE.

Short-course antibiotic treatment (2 weeks) has been investigated in right-sided *Staph. aureus* IE and in uncomplicated IE caused by viridans streptococcus, and has been found to be safe and efficacious in patients with IE without significant valvular complication. (Francioli, Ruch et al. 1995) Selected patients with streptococcal IE may also be suitable for once-daily dosing regimens with ceftriaxone, allowing consideration of outpatient treatment.

Table 8. Antimicrobial treatment for enterococcal, nutritionally variant and penicillin-resistant (MIC >0.5 mg/l) streptococcal infective endocarditis (IE)*

Condition	No allergy to penicillin Drug	Allergy to penicillin Drug	Duration
Enterococcal strain susceptible to penicillin, aminoglycosides, and vancomycin	Ampicillin + gentamicin or penicillin G + gentamicin	Vancomycin + gentamicin	4-6 weeks †
Enterococcal strain susceptible to penicillin, streptomycin, vancomycin, and resistant to gentamicin	Ampicillin + streptomycin or penicillin G + streptomycin	Vancomycin + streptomycin	4-6 weeks †
Enterococcal strain resistant to penicillin (intrinsic resistance), susceptible to gentamicin and vancomycin	Vancomycin + gentamicin	Vancomycin + gentamicin	6 weeks
Enterococcal strain resistant to penicillin (β-lactamase-producing), susceptible to gentamicin and vancomycin	Ampicillin-sulbactam + gentamicin	Vancomycin + gentamicin	6 weeks
Enterococcus faecalis resistant to penicillin, aminoglycosides and vancomycin	Imipenem + ampicillin or ceftriaxone + ampicillin	_	≥8 weeks
Enterococcus faecium resistant to penicillin, aminoglycosides and vancomycin	Linezolid or quinupristin-dalfopristin	Linezolid or quinupristin-dalfopristin	≥8 weeks

* Modified from Horstkotte, Follath et al. 2004 and Baddour, Wilson et al. 2005

† Duration of aminoglycoside administration could be shortened to 2-3 weeks, the total duration of treatment should be 6 weeks when vancomycin or teicoplanin are used

If blood cultures have been taken and empirical antibiotic treatment is considered necessary while awaiting the results, clues from predisposing factors and underlying medical conditions (invasive and dental procedures, IVDU, alcoholism, native versus prosthetic valve, interval since valvular surgery), as well as knowledge of local bactericidal resistance patterns, should be considered when choosing a regimen. In the subacute (lenta) type of IE, a combination of penicillin G and an AG can usually be recommended. In acute cases, the treatment should cover also *Staph. aureus*. If the

disease is hospital-acquired, due to intravenous lines or is a postoperative infection, vancomycin should be used to cover coagulase-negative staphylococci. The recommended empirical treatment of early PVE contains vancomycin together with rifampicin and an AG. For patients with PVE that begins 12 months or more after surgery, ceftriaxone could be added to cover HACEK-organisms. The therapy for PVE must be more intensive and prolonged (at least 6 weeks) because relapse and treatment failure rates are higher than in patients with NVE. (Baddour 1988)

Table 9. Antimicrobial treatment for staphylococcal infective endocarditis (IE)*

	No allergy to penicillin Drug	Allergy to penicillin Drug	Duration
Native valve IE			
Oxacillin-susceptible strain	Oxacillin + gentamicin	Cefazolin† + gentamicin or Vancomycin ± gentamicin	4-6 weeks (3-5 days aminoglycoside)
Oxacillin-resistant strain	Vancomycin	Vancomycin	4-6 weeks
Prosthetic valve IE			
Oxacillin-susceptible strain	Oxacillin + rifampicin + gentamicin	Vancomycin‡ + rifampicin + gentamicin	≥6 weeks combination (2 weeks aminoglycoside)
Oxacillin-resistant, gentamicin-susceptible strain	Vancomycin‡ + rifampicin¶ + gentamicin	Vancomycin‡ + rifampicin¶ + gentamicin	≥6 weeks combination (2 weeks aminoglycoside)

* Modified from Horstkotte, Follath et al. 2004 and Baddour, Wilson et al. 2005
† The use of cephalosporin is not recommended in patients with a history of anaphylactic reaction to penicillins
‡ Other choice teicoplanin
¶ If resistant to rifampicin, combine vancomysin with 1 or 2 other antistaphylococcal drugs, according to susceptibility pattern

Empirical therapy of culture-negative IE should initially target the most common fastidious organisms, including the HACEK group organisms. The treatment options for IE due to rare pathogens are presented in **Table 10**.

Table 10. Antimicrobial treatment for rare causes of infective endocarditis associated with negative blood cultures*

Pathogen	Drug	Duration
Brucella spp.	Doxycycline + rifampicin or cotrimoxazole	>3 months
Coxiella burnetii (Q-fever)	Doxycycline + hydroxycloroquine or doxicycline + fluoroquinolone	>18 months
Bartonella spp.	Ceftriaxone or doxicycline + aminoglycoside	6 weeks (2 weeks combination)
Chlamydia spp.	Doxycycline or new fluoroquinolones	Long term treatment, optimum duration unknown
Mycoplasma spp.	Doxicycline or new fluoroquinolones	>12 weeks
Legionella spp.	Macrolides + rifampicin or new fluoroquinolones	>6 months
Tropheryma whipplei	Cotrimoxazole or ceftriaxone + aminoglycoside	Long term treatment, optimum duration unknown

* Modified from Brouqui and Raoult 2001

2.9.3. Surgical therapy

2.9.3.1. Cardiac surgery

Several studies suggest that combined medical and surgical therapy can decrease mortality of IE. (Olaison and Pettersson 2002; Hasbun, Vikram et al. 2003) Surgery is required in 25-30% of cases during acute infection, and in 20-40% in later phases of IE. (Jault, Gandjbakhch et al. 1997) Indications for valvular surgery during the acute phase of IE are presented in **Table 11**. The optimal time to perform surgery is before severe hemodynamic disability or spread of the infection to perivalvular tissue has occurred. (Alexiou, Langley et al. 2000) For most stable patients, surgery is best delayed until the treatment with antibiotics is completed to reduce the risk of perioperative complications and early PVE.

Table 11. Indications for surgery in the acute phase of infective endocarditis*

Condition
• Congestive heart failure due to acute aortic or mitral regurgitation
• Hemodynamically significant prosthetic valve malfunction
• Evidence of perivalvular extension of infection
• Persistent infection after 7-10 days of adequate antimicrobial therapy
• Infections due to microorganisms with a poor response to antimicrobial therapy
• Recurrent emboli despite appropriate antimicrobial therapy
• Mobile vegetations >10 mm size during the first week of antimicrobial therapy
• Obstructive vegetations
• Early prosthetic valve endocarditis

* According to the guidelines of the European Society of Cardiology (Horstkotte, Follath et al. 2004)

CHF is the strongest indication for surgery in IE. Medically treated patients with moderate-to-severe CHF due to endocardits-related valvular dysfunction have a mortality rate of 56-86%, as compared with 11-35% among patients treated with combined medical and surgical therapy. (Croft, Woodward et al. 1983; Olaison and Pettersson 2002) According to Olaison (Olaison, Hogevik et al. 1996), the greatest benefit of acute surgery is gained by patients with heart failure with recent onset who undergo surgery soon (in their study by day 4). The mortality during treatment for these surgically and non-surgically treated patients was 0% versus 27%, and the cardiac mortality after 5 years follow-up was 0% versus 50%. Surgery is usually required in new aortic regurgitation due to IE. In contrast, mitral regurgitation can often be managed with medical therapy, and right-sided IE seldom requires surgery.

Abscess-formation is generally associated with a poor prognosis. Acute surgery is of doubtless benefit in most of these patients and a delay will compromise cardiac function and increase the peroperative risk. Uncontrolled sepsis or persistence of fever for more than 7 days despite maximal antimicrobial therapy due to any pathogen are usually an indication for surgery. Medical therapy for IE caused by some microorganisms is usually unsuccessful, and surgical therapy is generally advised. The pathogens include *P. aeruginosa*, *Brucella* spp., *Coxiella* spp., fungi and probably multiresistant enterococci, for which there is no synergistic bactericidal regimen, and MRSA. (Ellis, Al-Abdely et al. 2001)

In PVE, surgical treatment is usually considered and *Staph. aureus* PVE alone may be an indication for valve-replacement therapy. (John, Hibberd et al. 1998) Prosthesis dehiscence is an urgent indication for surgical therapy. When a device, such as a pacemaker or implantable defibrillator, is in place in a patient with IE, it often needs to be replaced as well, and this should be taken into consideration when planning the surgery. (Cacoub, Leprince et al. 1998)

Some authorities recommend surgery if there have been 2 episodes of embolization or one episode with residual large vegetations. (Mugge 1993) The risk of embolization increases if there are large vegetations (>10 mm), particularly at the mitral position, if the patient has PVE, if the cause is *Staph. aureus* infection and if the symptoms have had a short duration. The benefits of surgery in preventing further emboli are greatest if surgery is performed early in the course of IE. Patients with tricuspid valve vegetations >20 mm with a dilated right ventricle and recurrent pulmonary emboli or right-sided heart failure are also candidates for surgery. (Bayer, Blomquist et al. 1988; Hecht and Berger 1992) Of note, the persistence of vegetations, as determined by echocardiography, is not uncommon after successful medical treatment of IE and is not necessarily associated with late complications. (Vuille, Nidorf et al. 1994)

Because postoperative neurological deterioration or death may ensue, a recent neurological complication of IE has been considered a relative contraindication to valve-replacement surgery. A retrospective study of 181 patients with cerebral complications who underwent surgery for IE (Eishi, Kawazoe et al. 1995) found that the proportion of patients who had postoperative neurological deterioration (including death) depended on the interval between the preceding cerebral event and cardiac surgery. Among those who had non-hemorrhagic cerebral infarcts 7 days or less before surgery, neurological deterioration occurred in 44%; among those undergoing surgery 8 to 14 days after the CNS event, only 17% had neurological deterioration. The risk of a worsening of neurological deficit after cardiac surgery fell to 2% when the operation was performed 4 weeks or more after the CNS event. However, the risk of a worsening CNS deficit after cardiac surgery persisted for up to 4 weeks after intracerebral hemorrhage. Other studies have suggested that valve-replacement surgery carries no risk of neurological deterioration unless it follows intracerebral hemorrhage. (Ting, Silverman et al. 1991; Parrino, Kron et al. 1999) A conservative approach is to delay valve-replacement surgery, if feasible, for 2 to 3 weeks after an embolic infarction in the CNS, and for at least a month after intracerebral hemorrhage. (Eishi, Kawazoe et al. 1995; Gillinov, Shah et al. 1996)

Patients who are persistent drug abusers and have had repeated episodes of IE needing valve replacement surgery pose special ethical and practical problems, especially if they already have a prosthetic valve. However, IVDU is not a contraindication for surgery, per se.

The operation usually involves valve replacement with a metallic or biological prosthesis, but valve saving techniques with chordal preservation and partial leaflet resection are becoming more widespread. (Gillinov, Faber et al. 2002) Aortic IE requires implantation of a mechanical or biological prosthesis, the choice of which is made by the usual criteria: age and contraindications to long term anticoagulation.

Valve repair is sometimes possible when the affected valve is the mitral or the tricuspid valve. (Baumgartner, Omari et al. 2000) Mitral valve repair provides benefical short term and long term results in mitral valve IE. (Iung, Rousseau-Paziaud et al. 2004)

The duration of antimicrobial therapy after valve replacement surgery for active IE depends on the duration of the preoperative antimicrobial therapy, the presence of perivalvular extension of infection, and the microbiological and pathological findings at surgery. A full course of postoperative therapy is a reasonable approach to treat patients with a positive intraoperative culture or a myocardial abscess.

2.9.3.2. Non-cardiac surgery

Ruptured mycotic aneurysms in the brain may require neurosurgical intervention, including placement of coils or ligation. Arterial embolies to extremities disturbing blood flow may require urgent embolectomy. Splenectomy is associated with better survival than medical therapy alone in case of splenic abscesses. (Robinson, Saxe et al. 1992) Prosthetic joints are easily infected in IE and should be removed if any obvious purulent fluid collection occurs within the joint space or if marked loosening of prosthetic components occur.

2.9.4. Anticoagulant therapy

Anticoagulant therapy has not been shown to prevent embolism in IE, and may increase the risk of intracerebral hemorrhage. Patients with *Staph. aureus* PVE, who are receiving anticoagulant therapy, are particularly susceptible to CNS hemorrhage. (Tornos, Almirante et al. 1997; Roder, Wandall et al. 1999) In general, patients with PVE who require maintenance anticoagulation are cautiously given continued anticoagulant therapy during treatment of PVE but probably anticoagulation should be discontinued in all patients with *Staph. aureus* endocarditis until the septic phase of the illness has resolved. (Tornos, Almirante et al. 1999) If no CNS hemorrhage is present, heparin or low molecular weight heparin can be safely used in all IE patients.

In patients with prosthetic valves already in place, the average rate of major thromboembolism is about 8% per year. (Kearon and Hirsh 1997) There is therefore only a minor risk of valvular thrombosis by stopping warfarin for a short time. Anticoagulant therapy for NVE is restricted to patients with a clear indication separate from IE. In case of intracranial hemorrhage or mycotic aneurysm, anticoagulant therapy should be suspended until the complications are resolved.

2.10. Prophylaxis of IE

Prophylaxis against IE has become routine in most developed countries, although no prospective studies have proved that it is effective. (van der Meer, Thompson et al. 1992; Van der Meer, Van Wijk et al. 1992) By tradition, cardiac conditions associated with a certain risk for IE are grouped into 3 categories, namely cardiac disorders with high, moderate and low or negligible risk. (Dajani, Taubert et al. 1997) According to the Finnish recommendations (Lumio, Nieminen et al. 1995; Lumio, Vanhanen et al. 2006) and the guidelines of the European Society of Cardiology (Horstkotte, Follath et al. 2004), prophylaxis is recommended in patients with high risk and moderate risk

cardiac conditions (**Table 12**). In April 2007, the American Society of Cardiology issued new guidelines for the prevention of IE. (Wilson, Taubert et al. 2007) According to these guidelines, prophylaxis is recommended only in patients with cardiac conditions associated with the highest risk of adverse outcome from IE (**Table 12**).

Table 12. Cardiac conditions in which antimicrobial prophylaxis is indicated

Cardiac condition	Finnish guidelines*	ESC-guidelines°	AHA-guidelines§
High risk			
Prosthetic heart valves	X	X	X
Complex congenital cyanotic heart diseases	X	X	X†
Previous infective endocarditis	X	X	X
Surgically constructed systemic or pulmonary conduits	X	X	X
Heart transplantation recipients	X		X
Moderate risk			
Acquired valvular heart diseases	X	X	
Mitral valve prolapse with valvular regurgitation or severe valve thickening	X	X	
Non-cyanotic congenital heart diseases	X‡	X¶	
Hypertrophic cardiomyopathy		X	
Ablation therapy for atrial fibrillation	X♂		

* Hammasperäisen bakteeriendokardiitin antibioottiprofylaksi (Lumio, Vanhanen ym. 2006)
° Guidelines from the European Society of Cardiology (Horstkotte, Follath et al. 2004)
§ Guidelines from the American Heart Association (Wilson, Taubert et al. 2007)
† Unrepaired or incompletely repaired. If completely repaired, prophylaxis is recommended during the first 6 months after the procedure.
‡ Persistent ductus arteriosus and atrioventricular septal defect (ASD) during the first 6 months after closure
¶ Except for secundum type ASD
♂ During the first 6 months after therapy

Table 13. Diagnostic and therapeutic procedures in which prophylaxis is recommended

Predisposing diagnostic and therapeutic interventions	Finnish guidelines*	ESC-guidelines°	AHA-guidelines§
Oral cavity			
Dental procedures with risk of gingival or oral mucosal trauma	X†	X‡	X¶
Respiratory tract			
Tonsillectomy/adenoidectomy	X	X	
Bronchoscopy with rigid bronchoscope	X	X	
Gastrointestinal tract			
Sclerotherapy for esophageal varices	X	X	
Esophageal strictura dilatation	X	X	
Endoscopic retrograde cholangiography with biliary obstruction	X	X	
Biliary tract surgery	X	X	
Genitourinary tract			
Prostatic surgery	X	X	
Cystoscopy	X♂	X♂	
Urethral dilatation	X♂	X	
Vaginal hysterectomy	X		

* Suomalainen suositus endokardiittiprofylaksiasta (Lumio, Nieminen ym. 1995), Hammasperäisen bakteeriendokardiitin antibioottiprofylaksi (Lumio, Vanhanen ym. 2006)
° Guidelines from the European Society of Cardiology (Horstkotte, Follath et al. 2004)
§ Guidelines from the American Heart Association (Wilson, Taubert et al. 2007)
† Tooth extraction, periodontal surgery, scaling, removal of tartar, tooth inplantation
‡ Like † and root canal therapy
¶ All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa
♂ If urinary infection is present

The risk of bacteremia is highest in association with dental and oral procedures, intermediate with procedures that involve the genitourinary tract, and lowest with gastrointestinal procedures. (Durack 1995) **Tables 13** and **14** present the predisposing diagnostic and therapeutic interventions for which antimicrobial prophylaxis is recommended and those for which it is not recommended. Of note, according to the AHA-guidelines (Wilson, Taubert et al. 2007), prophylaxis is recommended only before dental procedures involving manipulation of gingival tissue or the periapical region of teeth or in case of perforation of the oral mucosa.

Table 14. Diagnostic and therapeutic procedures in which prophylaxis is not recommended

Predisposing diagnostic and therapeutic interventions	Finnish guidelines*	ESC-guidelines°	AHA-guidelines§
Oral cavity			
Dental procedures without risk of gingival or oral mucosal trauma	X	X	X
Respiratory tract			
Endotracheal intubation	X	X	X
Bronchoscopy with flexible device with or without biopsy	X†	X	X
Tympanostomy tube insertion	X	X	X
Gastrointestinal tract			
Transesophageal echocardiography	X	X	X
Endoscopy with or without gastrointestinal biopsy	X†	X	X
Genitourinary tract			
Vaginal hysterectomy		X	X
Vaginal delivery	X	X	X
Caesarean section	X	X	X
In uninfected tissue			
Urethral catheterisation	X	X	X
Uterine dilatation and curettage	X	X	X
Sterilization procedures	X	X	X
Insertion or removal of intrauterine devices	X	X	X
Other			
Cardiac catheterization with or without balloon angioplasty	X	X	X
Implantation of cardiac pacemakers, implantable defibrillators, and coronary stents	X	X	X

* Suomalainen suositus endokardiittiprofylaksiasta (Lumio, Nieminen ym. 1995), Hammasperäisen bakteeriendokardiitin antibioottiprofylaksi (Lumio, Vanhanen ym. 2006)
° Guidelines from the European Society of Cardiology (Horstkotte, Follath et al. 2004)
§ Guidelines from the American Heart Association (Wilson, Taubert et al. 2007)
† Prophylaxis is recommended only with biopsy

Prophylaxis is directed primarily against the viridanans streptococci and HACEK organisms before dental, oral, respiratory, and esophageal procedures, and against enterococci, *Strep. bovis*, and *Enterobacteriaceae* before genitourinary and lower gastrointestinal procedures. (Dajani, Taubert et al. 1997) For prophylactic reasons, antibiotics should be given 30-60 min before bacteremia is expected. Single-dose prophylaxis with amoxicillin is now widely accepted (**Table 15**).

There is no reason to expect that the incidence of IE can be reduced significantly by antimicrobial prophylaxis. At present, more episodes of IE are acquired by other mechanisms, such as open heart surgery, hemodialysis, long-term intravenous cannulation, and intracardiac devices, than by dental and endoscopic procedures. Also, prophylaxis with amoxicillin does not cover staphylococci, the most probable pathogens associated with nondental procedures. Therefore, primary prevention of IE

should target infected foci responsible for spontaneous bacteremia, especially poor dental hygiene. In addition, the resources should be directed towards early diagnosis of IE by liberal blood culture and echocardiography recommendations for febrile patients. (Horstkotte, Follath et al. 2004; Wilson, Taubert et al. 2007)

Table 15. Prophylactic antibiotic regimens in adults

	Finnish guidelines*	**ESC-guidelines°**	**AHA-guidelines§**
Dental, oral, respiratory and esophageal procedures			
Not allergic to penicillins			
Oral	Amoxicillin 2g	Amoxicillin 2g	Amoxicillin 2g
Unable to take oral medication	Ampicillin 2 g i.v.	Ampicillin 2 g i.v.	Ampicillin 2 g i.v.
			Or
			Cefazolin 1 g i.v. or i.m.
			Or
			Ceftriaxone 1 g i.v. or i.m.
Allergic to penicillins			
Oral	Roxitromycin 300 mg	Clindamycin 600 mg	Cephalexin 2 g
	Or	Or	Or
	Clarithromycin 800 mg	Azithromycin 500 mg	Clindamycin 600 mg
	Or	Or	Or
	Clindamycin 600 mg	Clarithromycin 500 mg	Azithromycin 500 mg
			Or
			Clarithromycin 500 mg
Unable to take oral medication	Vancomycin 1 g i.v.	Clindamycin 600 mg i.v.	Cefazolin 1 g i.v. or i.m.
			Or
			Ceftriaxone 1 g i.v. or i.m.
			Or
			Clindamycin 600 mg i.v.
Genitourinary and gastrointestinal procedures			
Not allergic to penicillins			
Oral	Amoxicillin 2 g	Amoxicillin 2g†	
Unable to take oral medication	Ampicillin 2 g i.v ± aminoglycoside, e.g. tobramycin 0.12 g	Ampicillin 2 g i.v ± gentamicin 1.5 mg/kg i.v. or i.m‡	
Allergic to penicillins			
Oral	Roxitromycin 300 mg	-	
	Or		
	Clarithromycin 800 mg		
	Or		
	Clindamycin 600 mg		
Unable to take oral medication	Vancomycin 1 g i.v. ± aminoglycoside e.g. tobramycin 0,12 g	Vancomycin 1 g i.v. ± gentamicin 1.5 mg/kg i.v. or i.m.‡	

¶ Single dose 30-60 min before procedure
* Suomalainen suositus endokardiittiprofylaksiasta (Lumio, Nieminen ym. 1995), Hammasperäisen bakteeriendokardiitin antibioottiprofylaksi (Lumio, Vanhanen ym. 2006)
° Guidelines from the European Society of Cardiology (Horstkotte, Follath et al. 2004)
§ Guidelines from the American Heart Association (Wilson, Taubert et al. 2007)
† Oral prophylaxis is not recommended in high risk cardiac conditions
‡ Gentamicin is recommended in high risk cardiac conditions

2.11. Relapse and recurrence of IE

Relapse of IE is defined as return of the original infection (same pathogen), and indicates treatment failure. It usually occurs within 2 months of discontinuation of antimicrobial therapy. The relapse rate of patients with NVE caused by penicillin-susceptible viridans streptococcus is generally less than 2% and 8-20% for enterococcal NVE. Among patients with IE caused by *Staph. aureus, Enterobacteriaceae*, or fungi, treatment failure is more probable and often occurs during the primary course of therapy. (Mylonakis and Calderwood 2001; Chang, MacDonald et al. 2003) A positive culture at the time of valve-replacement surgery, particularly in patients with staphylococcal endocarditis, is a risk for subsequent relapse. (Renzulli, Carozza et al. 2000) The relapse rate in PVE is approximately 10-15%. (Mylonakis and Calderwood 2001)

Recurrent IE is defined as a new episode of IE after the original episode has been cured. A previous history of IE is a well-documented risk factor for a new episode. During the first 5 years after an episode, 4% per year will experience a new bout of endocarditis. (Michel and Acar 1995) Recurrence after successful therapy is a frequent problem in patients with IVDU because of their drug seeking behavior and poor compliance with treatment, and drug rehabilitation is required. (Baddour 1988; Cherubin and Sapira 1993)

2.12. Mortality in IE

Despite advances in the diagnosis and management of IE, endocarditis is a disease that carries a high mortality. The in-hospital mortality rates 10-25% (**Table 1**), and 1-year mortality rates (30-40%) have changed little over the past 20 years. (Cabell and Abrutyn 2002; Hoen, Alla et al. 2002; Moreillon and Que 2004) Death results primarily from hemodynamic deterioration and CNS embolic events. The mortality rate related to IE among drug addicts is generally lower, approximately 10%. (Hecht and Berger 1992) This is explained by the fact that IE in IVDU patients is predominantly right-sided, which has a much better prognosis than left-sided IE, and the fact that patients with IVDU are generally much younger than IE patients without drug misuse.

The mortality rate among patients with IE varies according to the following factors: the causative microorganisms (4-16% mortality for viridans streptococci, 15-25% for enterococci, 25-47% for *Staph. aureus* and more than 50% for *P. aeruginosa*, *Enterobacteriaceae* and fungi), the presence of complications or coexisting conditions (for example CHF, neurological events, renal failure, or severe immunosuppression due to HIV-infection), the development of perivalvular extension, or a myocardial abscess, and the use of combined medical and surgical therapy in appropriate patients. (Watanakunakorn and Burkert 1993; Mylonakis and Calderwood 2001; Chu, Cabell et al. 2004)

Chu and collegues recently examined 267 consecutive patients with acute IE to determine factors early in the course of IE that were independently associated with mortality and found that the independent predictors of early mortality were diabetes

mellitus, *Staph. aureus* infection and an embolic event. (Chu, Cabell et al. 2004) According to Hasbun and colleagues (Hasbun, Vikram et al. 2003), 5 features at presentation that were independently associated with mortality at 6 months were abnormal mental status, comorbidities, moderate-to severe CHF, *Staph. aureus* infection and medical therapy without the use of surgery. Based on these findings, they were able to create a point-based classification system that accurately risk-stratified patients with IE; patients $\leq$6 points only had a 6% mortality at 6 months, while patients >15 points had a 63% mortality.

2.13. New developments

New avenues on how to prevent and treat IE are related to modifications of both the bacterium and the host. Vaccines and artificial peptides directed against specific bacterial adhesions could interfere with valve colonization. Encouraging clinical success has been reported with *Staph. aureus* conjugate vaccine in hemodialysis patients. (Shinefield, Black et al. 2002) Modified biomaterials with antiadherence properties are being sought as a means of preventing disease associated with prosthetic valves. (Schaff, Carrel et al. 2002) Also, new drugs with novel mechanisms of action are being investigated.

2.14. Conclusions

Improvements in population health and health care have reduced the classical forms of IE. Increased life expectancy and new medical and social behaviors have, however, generated a new group of at-risk patients. PVE, nosocomial endocarditis and endocarditis in drug addicts and hemodialysis patients are not due to classical streptococci, but rather to staphylococci, and occasionally also to Gram-negative bacteria and fungi. The apparent increase in IE associated with *Strep. bovis* in elderly patients could reflect a further epidemiological drift. (Hoen, Alla et al. 2002) Treatment of IE requires a multidisciplinary approach among health care providers with a variety of backgrounds. The same multidisciplinary approach should be used to guide the design of new clinical studies that should provide definite answers to several of the remaining questions about this complex disease.

3. AIMS OF THE STUDY

The purpose of this study was to evaluate the clinical presentation of infective endocarditis in patients treated in a Finnish teaching hospital during a period of 25 years.

The specific aims were:

1. To compare the von Reyn diagnostic criteria with the Duke diagnostic criteria in establishing the diagnosis of infective endocarditis
2. To assess the occurrence of neurological complications of infective endocarditis with special emphasis on comparing patients with and without such manifestations, and to evaluate which risk factors predict complications
3. To assess the usefulness of serum CRP and other markers of inflammation in monitoring the outcome of IE
4. To assess the value of direct amplification of rRNA genes from surgically removed valve tissue in the etiological diagnosis of infective endocarditis in a routine clinical setting
5. To evaluate the short-term and 1-year clinical outcome of the patients treated for infective endocarditis in a Finnish teaching hospital during 1980 - 2004
6. To evaluate what changes have taken place regarding infective endocarditis in our hospital during the study period of 25 years

4. SUBJECTS AND METHODS

4.1. Study subjects and data collection (I-VI)

Study subjects and study designs in publications I to VI are summarized in **Table 16**.

We reviewed the hospital files of all adult patients who were treated at the Department of Medicine, Turku University Central Hospital, Turku, Finland, during the years 1980-2004 for suspected or diagnosed IE. The hospital is a 1000-bed teaching facility with a cardiothoracic surgical department, serving as a tertiary referral centre for the south-western part of the country and as a primary care facility for infectious diseases for a region of about 200.000 inhabitants.

Table 16. Subjects and study designs in studies I-VI

Study	Time period	Patient population	Episodes (patients)	Purpose of the study
I	1980 – 1995	All suspected cases of infective endocarditis (IE)	243 (222)	Comparison of the von Reyn and the Duke criteria in the diagnosis of IE
II	1980 – 1996	Duke definite and possible cases	218 (200)	Evaluation of neurological manifestations in IE
III	1980 – 1999	Duke definite cases	134 (129)	Comparison of markers of inflammation in assessing the outcome of IE
IV	1994 – 2004	Patients undergoing surgery for IE who had valve samples analyzed by PCR	56 (56)	Evaluation of PCR in the etiological diagnosis of IE
V	1980 – 2004	Duke definite and possible cases	326 (303)	Evaluation of short-term and 1-year outcome of IE
VI	1980 – 2004	Duke definite and possible cases	326 (303)	Evaluation of epidemiology of IE

The clinical characteristics of these patients were assessed by reviewing their hospital charts. Data were collected on age, sex, fever and other classical clinical symptoms of IE, duration of symptoms, and administration of peroral antimicrobial therapy before admission. For each patient, the presence of predisposing heart conditions known to increase the risk for IE (Dajani, Bisno et al. 1990) were evaluated. Data were collected on various underlying diseases like diabetes, collagenosis, cancer, end-stage renal failure necessitating long term dialysis treatment, alcohol abuse, and IVDU. Preceding dental, surgical, and endoscopic procedures were registered, as were infections of the oral cavity and skin. Regarding physical examination, data were collected on fever and recognition of new valvular regurgitant murmurs on heart auscultation and specific vascular and immunologic manifestations suggesting IE (**Tables 3** and **4**). In addition, data on CRP, ESR, serum creatinine values, and WBC counts were registered.

Findings on echocardiography were evaluated. TTE was performed at least once during each episode, followed by TEE in 184 cases. Further, the patients were assessed for findings of blood cultures. For each blood culture bottle, 10 ml of blood had been collected and cultured as follows. Early in the study (1980 to 1985), double bottles [Supplemented Peptone Broth VACUTAINER (Beckton Dickinson, Rutherford N.J.,

USA)] for aerobic and anaerobic cultivation were used. Later (1986 to 1997), the lysis centrifugation method [Isolator (Du Pont & Nemours Inc., Wilmington, Del., USA)] was used, and the lysates were cultured both aerobically and anaerobically. Since 1997, the automated Bactec system (Becton Dickinson) with an aerobic and an anaerobic bottle per blood culture has been used. Identification of bacteria was performed according to standard microbiologic methods. The presence of clinical events including CHF, neurological complications and peripheral emboli were registered. The need for valvular surgery and mortality were recorded. For those patients who had undergone surgery or autopsy, histopathologic and microbiologic findings of the tissue specimens were registered.

4.2. Study I: Comparison of the Duke versus von Reyn criteria

Included were 222 patients treated during the years 1980-1995 for suspected or diagnosed IE. 16 patients had been treated for 2, one patient for 3 and one patient for 4 different episodes of suspected IE. Thus, the total number of episodes analyzed was 243. Each suspected case was retrospectively evaluated for the likelihood of IE using first the Duke and then the von Reyn diagnostic criteria.

4.2.1. Diagnosis of IE

4.2.1.1. Duke criteria

Using the Duke classification, the disease episodes were categorized as either definite or possible IE, or were rejected. The classification schema is described in detail in **Tables 3** and **4**. Briefly, evidence of endocardial involvement and typical blood culture are regarded as major criteria, while a predisposing cardiac condition or recent history of IVDU, the presence of fever $\geq 38.0^{o}C$, defined vascular and immunologic phenomena, intermittently positive blood cultures and echocardiographic findings consistent with IE but not meeting the major criteria are regarded as minor criteria. The disease is designated as definite IE, if a combination of a) 2 major criteria, b) 1 major and 3 minor criteria, or c) 5 minor criteria is fulfilled. The disease is categorized as definite IE also if histopathologic or microbiologic evidence of IE is obtained at surgery or autopsy. An episode of suspected IE is rejected, if i) a firm alternative diagnosis is established, ii) the symptoms of the patient resolute with antimicrobial therapy for 4 days or less, or iii) surgery or autopsy is performed within 4 days after commencing antimicrobial therapy and no pathologic evidence of IE is obtained. The case is classified as possible, if it can neither be rejected nor designated as definite IE.

4.2.1.2. von Reyn criteria

Using the von Reyn classification, the disease episodes were categorized either as definite, probable or possible IE, or were rejected. By these criteria, the disease is classified as definite IE only based on positive histopathologic or microbiologic findings from the affected valve or peripheral embolus. A disease episode is classified as probable or possible based on criteria in **Table 3**. Briefly, an episode is designated as probable IE if the patient has persistently positive blood cultures in association with a new regurgitant murmur or a predisposing heart condition combined with vascular phenomena. In case of negative or intermittently positive blood cultures, an episode is

designated as probable IE if the patient has fever combined with a new regurgitant murmur and vascular phenomena. An episode is classified as possible IE if the patient has persistently positive blood cultures and either a predisposing cardiac condition or vascular phenomena. In case of negative or intermittently positive blood cultures, a combination of a predisposing heart disease, fever and vascular phenomena is needed for the episode to be designated as possible IE. For viridans streptococcal cases, an episode is designated as possible, if the patient has fever and at least 2 positive blood cultures without an extracardiac source. Cases not fulfilling the above criteria are rejected as IE.

4.3. Study II: Neurological manifestations of IE

Included were 200 patients with 218 episodes of definite or possible IE according to the Duke criteria treated during the years 1980-1996. Comparison was made between episodes with neurologic manifestations and those without.

The neurological complications were classified into the following categories:

1) embolic brain infarction
2) transient ischemic attack (TIA)
3) cerebral hemorrhage
4) meningitis
5) brain abscess
6) toxic encephalopathy
7) headache

An embolic brain infarction was considered present if the patient had a focal neurological deficit persisting over 24 hours and a positive finding on the head CT scan or at autopsy. TIA was defined as focal neurological symptoms or signs lasting less than 24 hours and when a CT scan was either not done or the result was normal. The patient was diagnosed as having cerebral hemorrhage in case of acute neurological symptoms combined with a positive finding on the CT scan, at surgery, or at autopsy. Cases with ruptured mycotic aneurysms were included in this category. The diagnosis of meningitis required the presence of pleocytosis in the cerebrospinal fluid, but not necessarily positive findings in bacterial cultures. The diagnosis of a brain abscess required characteristic CT features of ring enhancement with surrounding edema or either a surgical or autopsy confirmation. Toxic encephalopathy was defined as mental changes or stupor without any focal neurological signs and without CT abnormalities. Headache was designated as a neurological manifestation only if it was severe and there was no indication of meningitis or apparent other cause.

4.4. Study III: Markers of inflammation in IE

Included were 129 patients treated during 1980-1999, in whom CRP was used as the main laboratory parameter to monitor the course of IE. The patients had 134 disease episodes designated as definite IE by the Duke diagnostic criteria. The course of IE was defined as complicated, if the patient had neurological manifestations or peripheral emboli, or needed cardiac surgery or died within 3 months.

Laboratory parameters
Serum CRP and ESR values, and WBC counts on admission and during the following 10 weeks were registered. The CRP values were examined several times during the first in-hospital week and, subsequently, at least 2 times a week. The values on admission, peak values during treatment, and the last values measured during week 1, 2, 3, 4, 6, 8 and 10 were included. A CRP concentration of <10 mg/l was considered normal. The reference values for the ESR were ≤20 mm/h for men and ≤30 mm/h for women and for WBC count 4.0-10.0x10^9/l for both genders.

4.5. Study IV: PCR in IE

Included were 56 valve samples from patients undergoing surgery during the years 1994-2004 for diagnosed or suspected IE. The samples were analyzed by PCR. Conventional microbiological methods were also used. (Kupila, Rantakokko-Jalava et al. 2003) The PCR assays were requested by the attending clinicians and performed at the Department of Medical Microbiology, University of Turku.

Data were collected on age, sex, blood culture findings, involved valves, preoperative CRP value, duration of preoperative antimicrobial therapy, indication for valve surgery, and microbiological and histological findings of the tissue specimens. Each case of IE was classified both preoperatively and postoperatively using the Duke diagnostic criteria. The recommendations of the American Heart Association (Wilson, Karchmer et al. 1995) and the European Society of Cardiology (Horstkotte, Follath et al. 2004) for the treatment of IE were used to assess whether the antimicrobial treatment given to each patient before surgery was adequate, i.e. effective and long enough towards the respective causative agent to constitute a complete course of IE. The clinical response to therapy was evaluated based on resolution of fever and normalization of the laboratory tests for inflammation. For the purposes of the present study, a patient was defined as having had adequate antimicrobial treatment before surgery, if the duration of the preoperative antimicrobial treatment effective for the causative agent was ≥28 days, the clinical symptoms of infection had resolved, and the preoperative CRP value was ≤15 mg/l.

4.5.1. DNA purification

DNA was extracted from the fresh tissue samples after proteinase K (0.1 mg/ml) digestion (56°C, 2 to 17 hours) with 2 phenol-chloroform-isoamyl alcohol extractions followed by one ether wash, as described earlier. (Jalava, Kotilainen et al. 1995)

4.5.2. PCR and sequencing

The primers, reagents, and conditions used in the broad-range bacterial 23S and 16S rDNA PCR assays have been described previously. (Kotilainen, Jalava et al. 1998) All samples were initially screened for the presence of bacterial DNA by amplification of the 23S rRNA gene with oligonucleotide primers MS 37 and MS 38. (Kotilainen, Jalava et al. 1998) Special care was taken to avoid carryover contamination of samples with amplicons. Strict measures were employed to separate the pre-PCR facilities from the post-PCR areas. Gamma irradiation was used to eliminate any remnants of environmental DNA from water, and UV light treatment of the PCR tubes containing

the final PCR mix was used before addition of template. (Kwok and Higuchi 1989; Nikkari, Merilahti-Palo et al. 1992) Inhibition of the PCR was ruled out by successful amplification of beta globin gene sequences. Bacterial identification was performed by sequencing of either or both of the partially amplified 23S or 16S rRNA genes. The 16S rDNA PCR product was preferred for sequencing because of the more abundant sequence data available in public databanks, whereas the 23S rDNA assay provided better sensitivity. Sequence analysis was performed as described previously. (Kotilainen, Jalava et al. 1998; Rantakokko-Jalava, Nikkari et al. 2000; Kupila, Rantakokko-Jalava et al. 2003)

4.6. Study V: Outcome of IE

Included were all 326 episodes treated during the years 1980-2004 fulfilling the Duke criteria for definite or possible IE. The presence of IE-associated neurological complications, peripheral emboli and heart failure were registered for each patient. Mortality and the need for surgical treatment were recorded in detail for all patients during a period of 1 year from admission. CRP, ESR and creatinine values and WBC counts on admission were also registered. The data were used to analyze the association between various patient and disease characteristics and the development of complications, mode of treatment and mortality of IE. The factors predicting short-term and 1-year clinical outcome and the requirement for surgical treatment were also delineated. Short-term outcome was defined as the outcome during the index hospitalisation.

4.7. Study VI: Epidemiology of IE

Included were the 326 episodes of definite or possible IE. For each patient, the presence of neurological complications, peripheral emboli and heart failure, as well as the need of cardiac surgery, and mortality of IE were recorded from the onset of symptoms to 3 months after the admission of the patient to hospital. The clinical characteristics of the episodes were analyzed both collectively and separately in 5-year study periods in order to define the potential changes in the clinical presentation of patients with IE treated in our hospital since 1980.

4.8. Statistical analyses

4.8.1. Studies I and II

Data were analyzed by the χ^2 test. A p-value less than 0.05 was considered statistically significant.

4.8.2. Study III

The differences between groups in the mean values of the CRP, ESR and WBC count peak recordings and the recordings on admission were statistically tested with the one-way analysis of variance (ANOVA). Tukey's multiple comparison correction technique was applied in post-hoc comparisons of ANOVA. Overall differences in the mean values and the changes in the mean values during the follow-up were tested using the analysis of variance of repeated measurements (RANOVA). (Crowder 1990) The normality of

residuals was evaluated graphically and with Shapiro-Wilk's test. Association of the CRP, ESR and WBC values at different time points with the outcome of the treatment or complications was analyzed using logistic regression analysis. The assumption of linearity in the logistic models was tested with Hoshmer-Lemeshaw lack of fit test. The overall accuracy of the laboratory tests in prediction of death was quantified with the area under receiver operating characteristic (ROC) curve. The ROC analysis was also used in the search of the cut-off points for prediction of death. (Hosmer and Lemeshow 2000) The difference in mortality or need for surgery between patients with normalized and elevated laboratory recordings after different treatment periods was tested using Fishers's exact test. The percentages of episodes with elevated CRP, ESR and WBC counts during the follow-up in different study groups were estimated with the Kaplan-Meier curves. The difference between curves was tested with log-rank test. (Collet 2003) In all tests, p values less than 0.05 were considered significant. All tests were 2-sided. The statistical computations were performed with SAS system for Windows, release 9.1/2004.

4.8.3. Study IV

Fisher's exact test and 2-tailed *t* test were used in statistical analyses.

4.8.4. Study V

The associations between the clinical characteristics and cumulative mortality or cumulative need for surgery was studied using survival (or event history) analysis. First, during different time periods the cumulative percentages for death or for need of surgery were estimated using Kaplan-Meyer technique. Differences in cumulative percentages between groups were tested using log-rank test. Differences between groups were quantified by calculating hazard ratios using Cox's regression models. Associations between in-hospital complications and death or need for surgery were tested using χ^2 test. P values less than 0.05 were considered as statistically significant. Statistical computations were carried out using SAS release 9.1/2005.

4.8.5. Study VI

The differences between the 5-year time periods in distributions of the categorical variables were statistically tested using Pearson's χ^2 test. Exact p-values were calculated in the case of small frequencies. The difference between time periods in the mean age was tested with one-way analysis of variance (ANOVA). The difference between blood culture groups and the change over time in the duration of the symptoms before admission were analyzed using Kruskal-Wallis test. P values less than 0.05 were considered statistically significant. Statistical calculations were performed with SAS System for Windows, release 9.1.3/2004.

5. RESULTS

5.1. Classification of IE (I)

Each of the 243 disease episodes in 222 patients treated in the hospital between 1980 and 1995 for suspected IE was retrospectively evaluated for the likelihood of IE using the Duke and the von Reyn diagnostic criteria. Of these episodes, 114 were designated as definite IE by the Duke criteria as compared with 64 episodes being so classified by the von Reyn criteria ($p<0.001$) (**Table 17**). 115 disease episodes were rejected by the von Reyn criteria, whereas only 37 episodes were rejected by the Duke criteria ($p<0.001$). Of the cases rejected by the von Reyn criteria, the Duke clinical criteria designated 6 (5%) as definite IE and 72 (63%) as possible IE.

Table 17. Categorization of 243 episodes of suspected or diagnosed infective endocarditis for the likelihood of infective endocarditis by the Duke versus von Reyn diagnostic criteria

	von Reyn criteria No. of episodes (%)					
Duke criteria	Definite	Probable	Possible	Rejected	Total	No. (%)
Definite	64	27	17	6	114	(47)
Possible	0	4	16	72	92	(38)
Rejected	0	0	0	37	37	(15)
Total	64 (26)	31 (13)	33 (14)	115 (47)	243	(100)

Among the histopathologically verified episodes, significantly more were designated as definite IE by the Duke clinical criteria as compared with a diagnosis as probable IE by the von Reyn criteria ($p=0.02$) (**Table 18**). 26 pathologically proven cases would have been rejected by the von Reyn criteria had surgery not been performed as compared with none being rejected by the Duke criteria ($p<0.001$). Of the 179 episodes without histopathologic verification, 50 were designated as definite IE by the Duke criteria compared with the diagnosis of probable IE in 31 episodes by the von Reyn criteria ($p=0.02$).

Table 18. Categorization of 64 histopathologically proven episodes of infective endocarditis for the likelihood of infective endocarditis by the Duke versus von Reyn diagnostic criteria, after exclusion of histopathological findings

	von Reyn criteria No. of episodes (%)				
Duke criteria	Probable	Possible	Rejected	Total	No. (%)
Definite	30	5	11	46	(72)
Possible	3	0	15	18	(28)
Rejected	0	0	0	0	(0)
Total	33 (51)	5 (8)	26 (41)	64	(100)

5.2. Complications of IE (II, V)

5.2.1. Neurological complications (II, V)

Neurological complications were identified in 55 (25%) of the 218 episodes treated between 1980 and 1996 (II), with an embolic event as the most frequent manifestation (23/55; 42%). In the majority (76%) of these episodes, the neurological manifestation was evident before antimicrobial treatment was started, and was the first sign of IE in 47% of episodes (**Figure 2**). Only one recurrent cerebral embolization was observed during that period. Neurological complications were significantly associated with the *Staph. aureus* etiology (29% versus 10%; p=0.001) and IE affecting both the aortic and mitral valves (56% versus 23%; p<0.01), but not with echocardiographic detection of vegetations or anticoagulant therapy. Death during the acute phase of IE occurred in 13 (24%) episodes with neurological complications and in 17 (10%) episodes without such complications (p<0.03). In episodes with neurological complications, the IE-associated mortality rate was 25% (10/40) in the medical treatment group and 20% (3/15) in the surgical group. No neurological deterioration was observed in these surgically treated patients postoperatively.

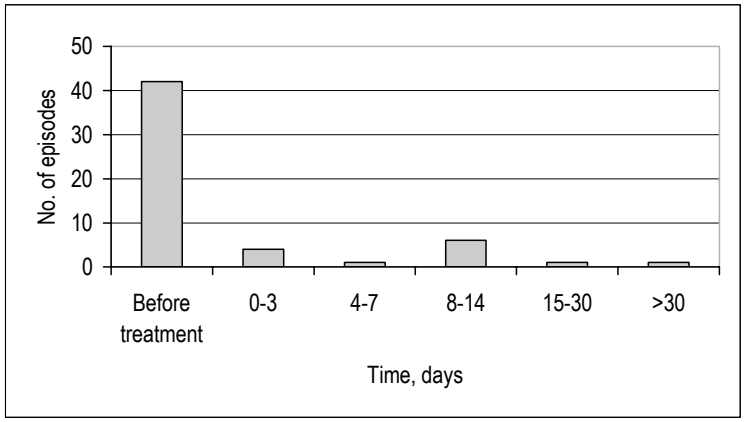

Figure 2. The timing of neurological manifestations during 55 episodes of infective endocarditis with neurological complications (Study II)

During the years from 1980 through 2004 (V), 86 (26%) of all 326 episodes had neurological complications (**Table 19**). The complication was manifested already on admission in 69% (59/86), within 1 week from admission in 77% (66/86), and within 2 weeks of admission in 86% (74/86) of the patients. There were significant differences in the development of neurological complications between IE caused by various microorganisms (p=0.035). Neurological complications were most common in episodes caused by *Strep. pneumoniae* and least common in blood culture-negative IE. Neurological complications were most common in infections of 2 native valves, and least common if only the tricuspid valve was infected, but the differences between infections of various valve sites were not significant. There was no difference in the frequency of all neurological events between the episodes with or without a vegetation, and with or without a major criterion detected on echocardiography.

Table 19. Distribution of neurological manifestations in 86 episodes of infective endocarditis with neurological complications (Study V)

Manifestation	No. of episodes	(%)
Embolic brain infarction*	27	(31)
Transient ischemic attack	16	(19)
Cerebral hemorrhage°	6	(7)
Meningitis	15	(17)
Brain abscess	2	(2)
Toxic encephalopathy	13	(15)
Headache	7	(8)
Total	86	(100)

* 9 associated with meningitis

° 1 associated with meningitis, 3 associated with a mycotic aneurysm

5.2.2. Heart failure and peripheral emboli (V)

CHF was the most frequent serious complication of IE and was detected in 55% (178/326) of all episodes. There were significant differences in the development of heart failure between the various microorganisms as causative agents and between the infected valve sites. Heart failure was most common in episodes caused by *Strep. pneumoniae* and in infection of 2 native valves, and least common in episodes caused by viridans streptococci and in tricuspid valve IE. Heart failure was significantly associated with an age ≥65 years.

Peripheral embolism including pulmonary emboli became manifest in 31% (102/326) of all episodes (**Figure 3**). The complication emerged already on admission in 56% (57/102), within 1 week from admission in 82% (84/102), and within 2 weeks from admission in 88% (90/102).

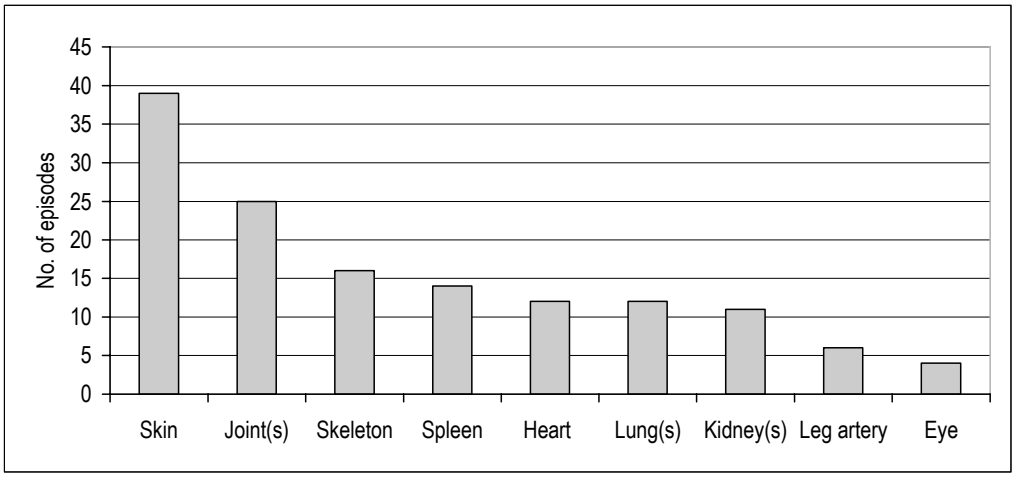

Figure 3. Distribution of peripheral emboli in 102 episodes of infective endocarditis with peripheral emboli

There were significant differences in the development of peripheral emboli among the causative agents and among the affected valves (p values <0.001). Peripheral emboli were most frequent in episodes caused by *Staph. aureus*, infection of 2 native valves or the tricuspid valve, and least common during episodes caused by coagulase-negative staphylococci and PVE. The occurrence of peripheral emboli was significantly associated with a vegetation detected on echocardiography (p<0.001), and with IVDU (p=0.012).

5.3. CRP, ESR and WBC for assessment of outcome of IE (III)

Extensive statistical analyses were used to evaluate the diagnostic usefulness of serial CRP, ESR and WBC determinations for monitoring the outcome of IE in 129 patients with 134 episodes of definite IE treated between 1980 and 1999. On admission, CRP was elevated in all episodes of IE, while ESR was normal in 14 (10%) episodes and the WBC count was normal in 47 (35%) episodes. The ESR values and WBC counts remained normal during the entire illness in 5 and 21 episodes of IE, respectively. All patients who died of IE had elevated CRP values before death, while 5 patients (19%) and 11 patients (41%) had normal ESR values and normal WBC counts, respectively, at the time of death.

High CRP and WBC count were significantly associated with a complicated course of IE and a fatal outcome; and high CRP, also with a need for cardiac surgery. The fall in serum CRP or WBC count was significantly faster when a patient had an uncomplicated recovery than when complications developed or death ensued, but this pattern did not emerge for ESR (**Figures 4** and **5**). None of the 80 patients in whom CRP was normalized within 10 weeks died of IE, and none of the 22 patients, in whom CRP was normalized within 4 weeks needed valve surgery. Of the 87 patients whose WBC count was normalized within 4 weeks, 6 died and 15 underwent valve surgery. A CRP level ≥62 mg/l after 4 weeks of therapy predicted death with a sensitivity of 86% and a specificity of 73%. A WBC count ≥7.1 x 10^9/l at the same time point predicted death with a sensitivity of 87%, but its specificity was only 52%.

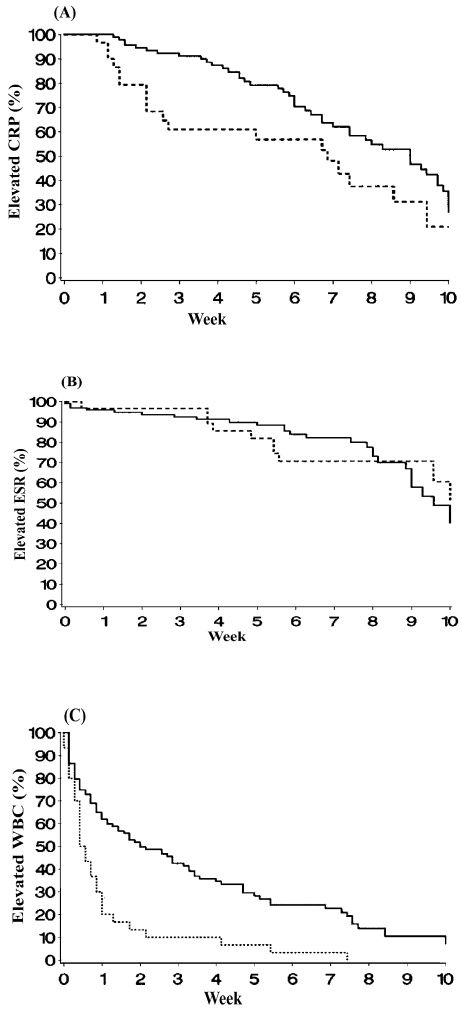

Figure 4. Kaplan-Meier estimates of the proportions of patients with elevated serum C-reactive protein values (A), erythrocyte sedimentation rates (B) and white blood cell counts (C). Lines are shown for patients with a complicated course (solid line) and an uncomplicated course (dotted line) of IE.

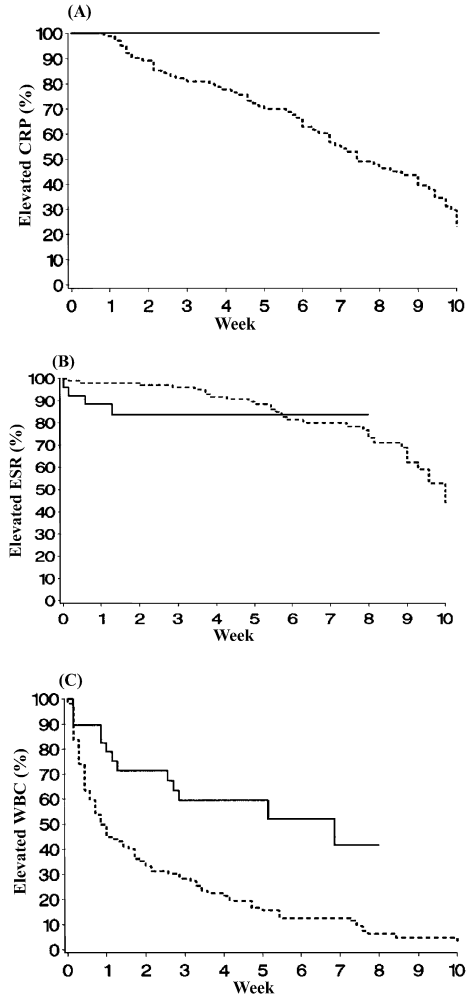

Figure 5. Kaplan-Meier estimates of the proportions of patients with elevated serum C-reactive protein values (A), erythrocyte sedimentation rates (B) and white blood cell counts (C) in patients with IE who died (solid line) and those who survived (dotted line).

5.4. Broad-range bacterial PCR for etiological diagnosis of IE (IV)

Broad-range PCR with primers targeting conserved bacterial rDNA sequences was applied to analyze directly valve samples from 56 patients operated on for diagnosed or suspected IE between 1994 and 2004. The final diagnosis was definite IE in 36 patients and possible IE in 2 patients, while the diagnosis of IE was rejected in 18 patients. PCR analysis from the removed valve tissue was positive in 25/38 patients with IE. Molecular identification was consistent with the blood culture finding in 20 of these patients. The PCR approach was the only method to yield the etiological diagnosis in

additional 4 patients (2 *Staphylococcus* spp., 1 *Strep. bovis*, 1 *B. quintana*), all of whom had received antimicrobials before blood cultures were taken. The mean duration of preoperative antimicrobial treatment for the patients with PCR-positive valves was 19.6 (range, 1-58) days. 13 patients with IE and all patients with no IE had no detectable levels of bacterial rDNA in their valves.

5.5. Surgical treatment of IE (V, VI, unpublished data)

5.5.1. Valve operations

Of all 326 episodes during the years 1980 through 2004, cardiac surgery was performed in 89 (27%) episodes during the initial hospitalization, in 94 (29%) episodes within 3 months and in 109 (33%) episodes within 1 year of hospital admittance (**Table 20**). Of these 109 operations, 39% (43/109) were performed within 14 days of admission; 15% (16/109) between 15 and 30 days of admission; and 32% (35/109) between 1 and 3 months of admission. Indications for heart surgery and types of the operations within 1 year are shown in **Tables 20** and **21**.

Table 20. Cumulation of indications for heart surgery within 1 year in 326 episodes of infective endocarditis

Indication of heart surgery	In-hospital	3 months	1 year
Congestive heart failure (CHF)	54	55	55
Valvular regurgitation without CHF	14	18	30
Dehiscence of prosthetic valve without CHF	10	10	10
Repeated emboli	5	5	6
Intractable infection	6	6	6
Valvular stenosis	0	0	2
Total	89	94	109

Table 21. Cumulation of operation types in patients requiring heart surgery within 1 year in 326 episodes of infective endocarditis

Operation type	In-Hospital	3 months	1 year
Mechanical prosthesis	72	75	87
Bioprosthetic valve	12	12	13
Mitral valvuloplasty	3	4	6
Other	2	3	3
Total	89	94	109

5.5.2. Factors predicting the need for in-hospital and 1-year surgery

Male sex and age ≤64 years significantly predicted a need for surgery at all time points, as did the development of CHF or the presence of a major criterion or vegetation on echocardiography (**Table 22).**

Table 22. Factors predicting the need for in-hospital and 1-year surgery in 326 episodes of infective endocarditis

	No. of episodes	Hazard ratio for in-hospital surgery	95% CI	p-value	Hazard ratio for surgery within 1 year	95% CI	p-value
Age				<0.001			<0.001
≥65 years	117	1			1		
18-64 years	209	3.03	1.76 - 5.21		2.57	1.59 - 4.13	
Sex				0.003			0.013
Female	92	1			1		
Male	234	2.30	1.32 - 4.02		1.83	1.14 - 2.95	
Etiology				0.611			0.178
Staphylococcus aureus	75	1			1		
CoNS*	31	1.17	0.52 - 2.63		1.07	0.49 - 2.36	
Viridans streptococci	67	1.55	0.82 - 2.96		1.56	0.88 - 2.77	
Enterococcus faecalis	28	0.59	0.20 - 1.76		0.53	0.18 - 1.56	
Streptococcus pneumoniae	11	1.59	0.53 - 4.76		2.67	1.07 - 6.65	
Other pathogens	25	1.28	0.55 - 2.97		1.30	0.61 - 2 77	
Culture negative	89	1.38	0.75 - 2.54		1.34	0.77 - 2.35	
Affected valve				<0.001			0.002
Prosthetic	67	1			1		
Aortic	113	1.41	0.82 - 2.42		1.47	0.87 - 2.48	
Mitral	96	0.30	0.14 - 0.65		0.67	0.37 - 1.22	
Tricuspid	18	NA°	NA°		NA°	NA°	
Two native valves	32	1.77	0.90 - 3.49		2.22	1.16 - 4.25	
Echocardiographic findings							
Major Criterion				0.004			<0.001
No	105	1			1		
Yes	221	2.99	1 63 - 5.50		2.57	1.58 - 4.18	
Vegetation				0.027			0.007
No	128	1.			1		
Yes	198	1.71	1.06 - 2.76		1.76	1.17 - 2.66	
Neurological complication				0.399			0.184
No	240	1			1		
Yes	86	1.22	0.77 - 1.94		1.32	0.88 - 1.99	
Peripheral emboli				<0.001			0.112
No	224	1			1		
Yes	102	6.12	3.97 - 9.42		1.37	0.93 - 2.03	
Heart failure				<0.001			<0.001
No	148	1			1		
Yes	178	2.26	1.42 - 3.59		2.27	1.52 - 3.39	

* Coagulase-negative staphylococci
° Not available

Peripheral emboli predicted a need for in-hospital surgery, while *Strep. pneumoniae* as a causative agent and infection of 2 native valves predicted a need for surgery within 1 year from admission.

5.6. Outcome of the patients with IE (V, unpublished data)

5.6.1. Mortality

Within 1 year, 80 patients died, 53 of them of IE. IE-associated in-hospital mortality was 14% (46/326), and mortalities within 1 month, 3 months and 1 year were 7% (23/326), 13% (43/326) and 17% (53/326), respectively. The principal cause of death of IE was cardiac in 72% (38/53) and neurological in 13% (7/53) of episodes and resulted from septicemia and multi organ failure in 11% (6/53). In 2 episodes (4%), death occurred during valve surgery (**Table 23**).

Table 23. Cumulative mortality within 1 year in 326 episodes of infective endocarditis

Cause of death	3 months	In-hospital	1 year
Infective endocarditis	43	46	53
Cardiac	32	33	38
Neurological	5	6	7
Septicemia and multi organ failure	4	5	6
Death during operation	2	2	2
Other causes	10	11	27
Total	53	57	80

5.6.2. Factors predicting short-term and 1-year outcome

All 326 episodes of IE were evaluated for short-term and 1-year outcome with the aim to define the factors predicting the prognosis of IE. The in-hospital mortality related to episodes treated with antimicrobials combined with in-hospital surgery was 17% (15/89) and it was 13% (31/237) in episodes treated only medically (p=0.751). This non-significantly higher mortality in operated patients persisted for up to 1 year from admittance. Infection of 2 native valves and the occurrence of neurological complications, peripheral emboli, or heart failure significantly predicted both in-hospital and 1-year mortality, while age ≥65 years or the presence of a major criterion or vegetation on echocardiography predicted death within 1 year (**Table 24**). There was a significant association between the level of serum CRP on admission and both the short-term and the 1-year outcome. In the patients who had CRP values ≥100 mg/l on admission, the hazard ratio for in-hospital death was 2.9-fold and the hazard ratio for 1-year death was 3.9-fold as compared to those with lower CRP values.

Table 24. Factors predicting in-hospital and 1-year mortality in 326 episodes of infective endocarditis

	No. of episodes	Hazard ratio for in-hospital death	95% CI	p value	Hazard ratio for death within 1 year	95% CI	p value
Age				0.068			0.005
18-64 years	209	1			1		
≥65 years	117	1.72	1.0 –3.03		2.17	1.27 -3.70	
Sex				0.426			0.707
Female	92	1			1		
Male	234	1.32	0.67 -2.60		1.12	0.61 -2.10	
Etiology				0.060			0.066
Staphylococcus aureus	75	1			1		
CoNS*	31	0.87	0.33 -2.26		0.93	0.36 -2.40	
Viridans streptococci	67	0.90	0.40 -2.03		0.85	0.40 -1.81	
Enterococcus faecalis	28	0.36	0.08 -1.57		0.55	0.16 -1.90	
Streptococcus pneumoniae	11	2.37	0.85 -6.59		2.58	0.94 -7.09	
Other pathogens	25	0.35	0.08 -1.54		0.31	0.07 -1.36	
Culture negative	89	0.42	0.17 -1.05		0.51	0.23 -1.13	
Affected valve				<0.001			<0.001
Prosthetic	67	1			1		
Aortic	113	1.13	0.48 -2.65		1.01	0.46 -2.19	
Mitral	96	0.45	0.16 -1.31		0.60	0.24 -1.47	
Tricuspid	18	1.04	0.22 -4.88		0.73	0.16 -3.35	
Two native valves	32	3.55	1.49 -8.47		3.75	1 68 -8.34	
Echocardiographic findings							
Major Criterion				0.346			0.015
No	105	1			1		
Yes	221	1.43	0. 68 -3.00		2.44	0.19 -5.0	
Vegetation				0.102			0.005
No	128	1.			1		
Yes	198	1.81	0.90 -3.68		2.62	1.35 -5.09	
Neurological complication				0.009			0.003
No	240	1			1		
Yes	86	2.17	1.21 -3.90		2.30	1.34 -3.96	
Peripheral emboli				0.036			0.016
No	224	1			1		
Yes	102	1.86	1.04 -3.33		1.95	1.14 -3.35	
Heart failure				<0.001			<0.001
No	148	1			1		
Yes	178	5.98	2.35 -15.17		7.62	3.26 -17.83	
Serum CRP on admission				0.008			<0.001
<100 mg/l	124	1			1		
≥100 mg/l	148	2.92	1.33 -6.40		3.90	1.81 -8.43	

***** Coagulase-negative staphylococci

5.7. Changes in epidemiology of IE (VI)

The 326 episodes of IE were evaluated for clinical characteristics and their changes over time. **Figure 6** presents the essential clinical symptoms of the whole patient population.

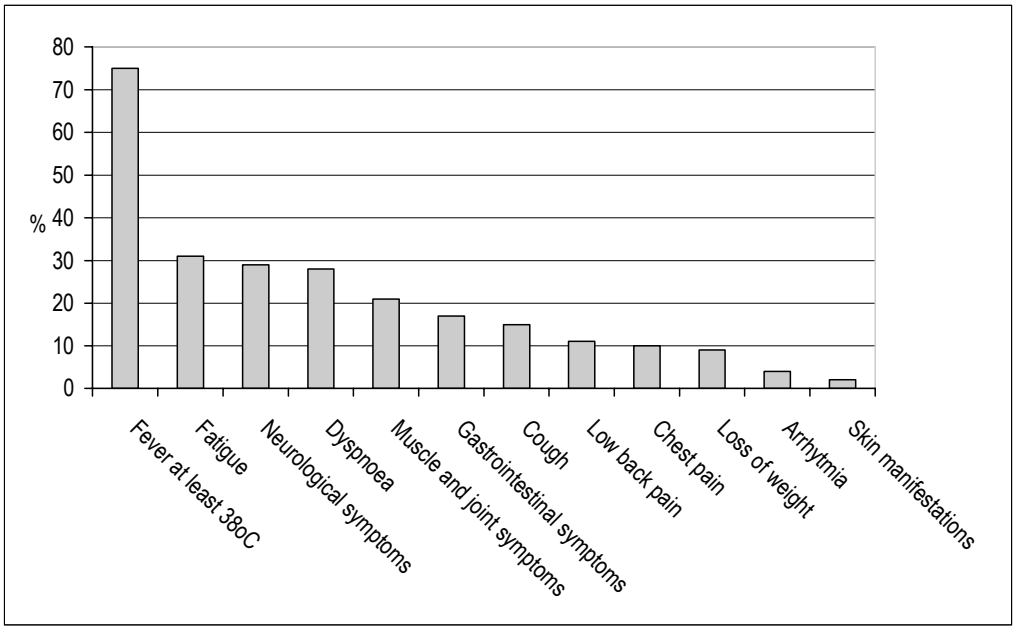

Figure 6. Symptoms of infective endocarditis in 326 episodes of infective endocarditis

When analyzed in 5-year periods, the number of episodes increased over time from 61 episodes during 1980-1985 to 95 episodes during 2000-2004 ($p<0.001$) (**Table 25**). The mean age of the patients rose from 47 to 54 years ($p=0.003$). During the study period, 25 (8%) episodes were associated with IVDU, with a significant increase of these episodes after 1996 ($p<0.001$). Viridans streptococci were the most common causative agents of IE during 1980-1994, but after that, *Staph. aureus* was the most common pathogen ($p=0.015$). The proportion of IE of the aortic valve decreased during the study, while the proportions of mitral and tricuspid valve IE increased correspondingly ($p=0.001$). Chronic dialysis for renal failure as an underlying condition increased over the years ($p=0.015$), but there were no changes in any other predisposing conditions. Complications, such as neurological manifestations and heart failure, did not change in frequency, but the incidence of lung emboli increased ($p<0.001$); 83% of these emboli occurred in patients with IVDU. There was no change in the proportion of patients requiring surgical treatment within 3 months, or in mortality of IE. CHF was the main indication for surgery during the whole 25-year study.

Table 25. Characteristics of 326 episodes of IE analyzed together and separately in 5-year periods

	1980-2004	1980-4	1985-9	1990-4	1995-9	2000-4	p value
No of episodes	326	61	45	65	60	95	<0.001
Sex							0.336
Male	234 (72%)	48 (79%)	30 (67%)	43 (66)%	47 (78%)	66 (70%)	
Female	92 (28%)	13 (21%)	15 (33%)	22 (34%)	13 (22%)	29 (31%)	
Mean (SD) age years	54.4 (17%)	47.2 (18%)	54.0 (16%)	59.4 (12%)	56.3 (17%)	54.5 (20%)	0.003
Affected valves							0.001
Aortic	113 (35%)	30 (49%)	15 (33%)	26 (40%)	16 (27%)	26 (27%)	
Mitral	96 (30%)	11 (18%)	10 (22%)	22 (34%)	20 (33%)	33 (35%)	
Tricuspid	18 (6%)	0%	1 (2%)	0%	4 (7%)	13 (14%)	
Two native valves	32 (10%)	6 (10%)	6 (13%)	3 (5%)	9 (15%)	8 (8%)	
Prosthetic valve(s)	67 (21%)	14 (23%)	13 (29%)	14 (22%)	11 (18%)	15 (16%)	
Blood cultures							0.163
Staphylococcus aureus	75 (23%)	7 (12%)	7 (16%)	12 (19%)	18 (30%)	31 (33%)	
CoNS*	31(10%)	7 (12%)	3 (7%)0	9 (14%)	4 (7%)	8 (8%)	
Viridans streptococci	67 (21%)	11 (18%)	9 (20%)	14 (22%)	14 (23%)	19 (20%)	
Enterococcus faecalis	28 (9%)	10 (16%)	5 (11%)	3 (5%)	4 (7%)	6 (6%)	
Streptococcus pneumoniae	11 (3%)	2 (3%)	1 (2%)	2 (3%)	2 (3%)	4 (4%)	
Other	25 (8%)	6 (10%)	2 (4%)	3 (5%)	4 (7%)	10 (11%)	
Negative	89 (27%)	18 (30%)	18 (40%)	22 (34%)	14 (23%)	17 (18%)	
Echocardiographic findings							<0.001
Major	221 (68%)	35(58%)	22 (49%)	44 (68%)	46 (77%)	74 (78%)	
Minor	60 (18%)	8 (13%)	13 (29%)	17 (26%)	7 (12%)	15 (16%)	
No findings	45 (14%)	18(30%)	10 (22%)	4 (6%)	7 (12%)	6 (6%)	
Cardiac conditions							0.491
Acquired valve disease	75 (23%)	17 (28%)	8 (18%)	15 (23%)	13 (22%)	22 (23%)	
Prosthetic valves	67 (21%)	14 (23%)	13 (29%)	14 (22%)	11 (18%)	15 (16%)	
Bicuspid aortic valve	38 (12%)	9 (15%)	6 (13%)	7 (11 %)	6 (10%)	10 (11%)	
Mitral valvular prolapse	33 (10%)	2 (3%)	4 (9%)	11 (17%)	7 (12%)	9 (10%)	
Congenital heart disease	10 (3%)	3 (5%)	2 (4%)	3 (5%)	0 %	2 (2%)	
No underlying cardiac condition	103 (32%)	16 (26%)	12 (27%)	15 (23%)	23 (38%)	37 (39%)	
IVDU	25 (8%)	0%	0%	0%)	6 (10%)	19 (20%)	<0.001
Dialysis	10 (3%)	0%	0%	0%)	3 (5%)	7 (7%)	0.015

* Coagulase-negative staphylococci

6. DISCUSSION

6.1. Diagnostic classification of IE (I)

The Duke criteria for the diagnosis of IE were introduced a few years before the present study was initiated (Durack, Lukes et al. 1994), but at first, the value of these criteria was unestablished. This new classification system afforded a major advantage as compared to all older criteria: a case could be designated as definite IE also based on clinical findings and echocardiographic results. Therefore, the first aim of the present work was to validate the Duke diagnostic criteria in a clinical patient population by evaluating 243 episodes of suspected IE treated in one teaching hospital during 1980-1995 for the likelihood of IE using the new Duke criteria and the older von Reyn citeria. Based on the results, a significantly higher proportion of all disease episodes were designated as definite IE, and significantly fewer episodes were rejected by the Duke criteria than by the von Reyn criteria. The Duke criteria also designated a significantly higher proportion of the episodes which were not pathologically proven as definite IE than were designated as probable IE when the von Reyn criteria were used. These results show that the Duke criteria are more sensitive than the von Reyn criteria and corroborate the findings of some previous studies. (Bayer, Ward et al. 1994; Durack, Lukes et al. 1994; Olaison and Hogevik 1996)

In this study, objective evidence on the significantly higher sensitivity of the Duke criteria was obtained also by reclassifying all episodes with histopathologic verification of IE by clinical and echocardiographic findings alone. A total of 46 of the 64 pathologically proven cases were designated here as definite IE by the Duke clinical criteria, while 33 were classified as probable IE by the von Reyn criteria. Assuming the category "definite" of the Duke clinical criteria to be analogous to the category "probable" of the von Reyn criteria, the sensitivities of these 2 classification systems were 72% and 52%, respectively ($p=0.02$). These results are consistent with those reported by Durack et al. (Durack, Lukes et al. 1994)

In the patient population, the Duke criteria rejected only one third of the cases rejected by the von Reyn criteria. Moreover, as many as 26 histopathologically proven cases would have been rejected by the von Reyn criteria had surgery not been performed. This is in agreement with previous studies focusing on the diagnosis of IE by the Duke versus von Reyn criteria, in which a lower proportion of the episodes of suspected IE, whether with or without pathologic verification, has been rejected by the Duke criteria. (Bayer, Ward et al. 1994; Durack, Lukes et al. 1994; Olaison and Hogevik 1996)

The inclusion of certain echocardiographic findings and knowledge of predisposing intravenous drug abuse in the Duke criteria can be considered as the main improvement to the older criteria. However, when the Duke criteria were first introduced, they were severely criticized by many authorities for lending so much weight to the echocardiographic findings, despite their potential insensitivity and unspecificity. (von Reyn and Arbeit 1994) It can now be admitted that at that time, the diagnostic accuracy of echocardiography was, indeed, unsatisfactory. In recent years,

however, the diagnostic accuracy has markedly improved by utilization of the transesophageal examination technique with the detection rates of vegetations between 82% and 94%. (Mugge, Daniel et al. 1989; Shively, Gurule et al. 1991; Birmingham, Rahko et al. 1992; Shapiro, Young et al. 1994; Werner, Schulz et al. 1996) Today, it seems quite logical to delineate certain echocardiographic findings as major diagnostic criteria, since echocardiography constitutes the basic diagnostic tool in patients with suspected endocarditis.

Before the present study, the Duke criteria were validated in 2 different patient populations, one described by Bayer et al. (Bayer, Ward et al. 1994) treated in a municipal hospital in the USA and the other described by Olaison et al. (Olaison and Hogevik 1996) treated in a tertiary referral center in Sweden. In the series of Bayer et al., half of the patients were intravenous drug abusers. In the Swedish series, 4% of the patients had a history of recent IVDU, while none of the patients included in the present study were drug abusers. Together, these 2 Scandinavian studies validate the use of the Duke classification system also in patients with no or very uncommon IVDU. Currently, the Duke criteria are generally well accepted to be used both clinically and in research work. Recently, proposed modifications have been published (Lamas and Eykyn 1997; Li, Sexton et al. 2000). So far, these modifications have not been tested in our patient population.

6.2. Complications of IE (II, V, VI)

6.2.1. Neurological complications (II, V, VI)

The incidence of neurological manifestations and the distribution of various complications in our patient population (II, V, VI) are consistent with earlier reports. (Salgado, Furlan et al. 1989; Kanter and Hart 1991) Also in the present study, an embolic event leading to ischemic stroke or TIA was the most common neurological manifestation. The occurrence of neurological complications in patients with IE is known to be associated with an adverse outcome. Corroborating the results of many previously published papers (Jones, Siekert et al. 1969; Pruitt, Rubin et al. 1978; Davenport and Hart 1990), the mortality was here significantly higher in those patients who had neurological complications than in those with no such complications [at 3 months, 24% versus 10%, $p<0.03$ (II) and 23% versus 10%, $p=0.003$ (V)]. Accordingly, the results of the present work support the theory that the overall prognosis of IE could be improved, if the occurrence of neurological complications could be reduced.

Yet, it is difficult to reduce the incidence of these complications, since most of them are present on the admission of the patient or develop during the early hospital stay. (Davenport and Hart 1990; Roder, Wandall et al. 1997) A neurological manifestation was the first sign of IE in 47% among the patients in study II. Moreover, recurrent neurological events are known to be uncommon. (Davenport and Hart 1990; Hart, Foster et al. 1990; Roder, Wandall et al. 1997) This is consistent with the finding of the present study of only one recurrence in the 53 patients with neurological manifestations (II). The probability of these complications decreases rapidly after commencement of antimicrobial treatment, presumably due to stabilization of the vegetations during the

healing process. (Vuille, Nidorf et al. 1994) Also this tendency was verified in the present study, with only 24% (II) and 31% (V) of the neurological complications becoming manifest after antimicrobial treatment was started. Collectively, these data indicate that a rapid diagnosis and initiation of antimicrobial therapy are the best ways to prevent the development of neurological complications and to improve the prognosis of the patients with IE.

In the present study, there was no difference in the occurrence of neurological complications between the patients with or without echocardiographically identifiable vegetations. [53% and 45% (II); 29% and 22% (V)]. However, a number of other studies have shown that the frequency of major embolic events is significantly higher in patients with vegetations on echocardiography than in those with no vegetations. (Cabell, Pond et al. 2001; Granowitz and Longworth 2003; Thuny, Di Salvo et al. 2005) Moreover, the size and nature of the vegetation may be of even greater importance than the mere presence or absence of a vegetation. According to Mügge et al. (Mugge, Daniel et al. 1989), patients with large (diameter >10 mm) vegetations have a significantly higher incidence of embolic events than those with smaller vegetations, particularly in the subgroup of patients with native mitral valve infection.

Opinion has differed as to whether surgery is required to prevent recurrent stroke in patients with embolic events. At the present time, many authorities agree that one episode of embolization is usually not an indication for valve replacement. This policy is supported by the infrequent nature of recurrent emboli after antimicrobial therapy has been started. (Hart, Foster et al. 1990; Steckelberg, Murphy et al. 1991) For example, only one recurrent cerebral embolization occurred in the patients of this study (II). According to recent guidelines, large vegetations with a diameter over 10 mm may be an indication for early valve surgery. (Horstkotte, Follath et al. 2004; Horstkotte and Piper 2006) In none of the present patients was a vegetation considered the main indication for operative treatment (II, V). In several of them, however, the presence of a vegetation may have been an additional factor contributing to the decision to operate.

A recent neurological complication of IE has been considered to be a relative contraindication for valve replacement surgery, because heparinization and hypotension during open heart surgery potentially aggravate the neurological injury. (Tunkel and Kaye 1993) However, the occurrence of neurological deterioration after surgery may be dependent of the nature of the complication and the interval between the complication and cardiac surgery. In a retrospective study of 181 patients with CNS complications, neurological deterioration occurred in 44% of the patients who were operated on within 7 days from non-hemorrhagic cerebral infarcts but in only 17% of those undergoing surgery between 8 and 14 days after the CNS event. (Eishi, Kawazoe et al. 1995) Later, Jault et al. (Jault, Gandjbakhch et al. 1997) have reported on 247 patients who were operated on for active NVE: the preoperative neurological complications diagnosed in their 26 patients had no influence on operative mortality. The authors postulate that the favorable result may be explained by their practice to delay the operation in patients with a brain hemorrhage. There are other studies suggesting that valve replacement surgery carries no risk of neurological deterioration unless it follows intracerebral hemorrhage. (Ting, Silverman et al. 1991; Parrino, Kron

et al. 1999) In the present work (II), the patients with neurological complications who were treated surgically had a slightly better outcome than those who were treated conservatively, with the respective IE-associated mortality rates of 20% and 25%. Although the surgical mortality of the patients with neurological complications was higher than of those free of such complications, this was probably due to a more severe disease in the former group, indicated by the higher proportion of patients with *Staph. aureus* IE and involvement of both left-sided valves. Moreover, all surgically treated patients with a fatal outcome died of cardiac causes and none of the survivors exhibited neurological deterioration postoperatively. Collectively, these data support the concept that a patient should not be denied cardiac surgery merely on the basis of a neurological event. (Parrino, Kron et al. 1999) Yet in patients with IE-associated intracranial hemorrhage, it is obviously sensible to postpone surgery due to the high risk of fatal complications, for at least one month after the hemorrhage. (Eishi, Kawazoe et al 1995; Gillinow et al 1996)

Per oral anticoagulant therapy at the time of diagnosis of IE has been reported to be associated with an adverse outcome. (Tornos, Almirante et al. 1999) When analyzing 56 patients with left-sided *Staph. aureus* IE, Tornos et al. noticed that per oral anticoagulant therapy was closely associated with death due to neurological damage. On this basis, they recommend that as soon as this diagnosis is indicated, the use of anticoagulant therapy should be immediately stopped until the septic phase of the disease is overcome. We made efforts to evaluate the association between administration of anticoagulants and the prognosis of IE but failed to confirm the unfavorable effect of anticoagulant therapy in our patients (II). According to the current recommendations, patients with PVE who require maintenance anticoagulation can be cautiously given anticoagulant therapy during the treatment of PVE but it should be probably discontinued during the acute phase of *Staph. aureus* IE. On the other hand, it is considered that if no CNS hemorrhage is present, heparin or low molecular weight heparin can be safely used in all patients with IE.

6.2.2. Heart failure and peripheral emboli (V)

Consistent with many recent reports (Hoen, Alla et al. 2002; Mouly, Ruimy et al. 2002; Cecchi, Forno et al. 2004), CHF was here the most common complication of IE, occurring in over 50% of all episodes. Peripheral embolism was the second most common complication, and was encountered in 30% of the episodes. As many as 60% of all peripheral emboli were manifested before hospital admission and could thus not be prevented. In line with previous reports (Thuny, Di Salvo et al. 2005), peripheral emboli were most common in those episodes of IE, which were caused by *Staph. aureus.* Unlike neurological manifestations, peripheral emboli were associated with vegetations shown in echocardiography.

6.3. CRP for assessment of outcome of IE (III)

In this study, extensive and modern statistical analyses were performed to evaluate the diagnostic utility of CRP and various other markers of inflammation in patients treated for IE. High CRP values and high WBC counts were significantly associated with a complicated course of IE and fatal outcome; and high CRP also with a need for cardiac

surgery. These results corroborate the only previous study in which statistical analyses were employed to evaluate the clinical utility of serial CRP and WBC determinations in the assessment of disease severity and outcome of patients with IE. (Olaison, Hogevik et al. 1997) In that study, a total of 167 episodes of definite IE treated in a Swedish university hospital were examined, and statistically significant differences were observed in the serial levels of CRP and WBC between complicated and uncomplicated course of IE. A trend towards higher concentrations of serial serum CRP values in patients with IE-related complications has been described also in the few other studies focusing on this issue but involving a relatively small number of patients and limited or no statistics. (Roberts-Thomson, Koh et al. 1986; McCartney, Orange et al. 1988; Chao, Liu et al. 1991)

During the course of endocarditis, the patients' responses to therapy were successfully monitored by serial determinations of CRP. Throughout the disease, the fall in the serum CRP concentration was significantly faster when a patient had an uncomplicated recovery of IE than when complications developed or death ensued. These results validate observations made in earlier studies that a progressive decline of CRP towards normal reflects a favorable response to antimicrobial therapy, whereas a sustained elevation of CRP implies failure of therapy. (Roberts-Thomson, Koh et al. 1986; McCartney, Orange et al. 1988; Chao, Liu et al. 1991; Olaison, Hogevik et al. 1997) This is further supported by the finding that preoperative CRP values were significantly higher in the patients with cardiac abscesses found at surgery than in those in whom abscesses were not found.

Normalization of the CRP value was invariably associated with a good prognosis for the patients treated at the Turku University Central Hospital in 1980-1995. This is the most important finding of Study III. In fact, none of the 80 patients who had normal CRP by week 10 died of IE and none of the 22 patients whose CRP was normalized by week 4 needed cardiac surgery, and only 2 of the 33 patients whose CRP normalized by week 6 needed cardiac surgery, both in spite of the fact that the medical treatment of IE was successful. Based on these findings, a normal CRP value may be clinically the most useful laboratory finding during the treatment of IE, since it demonstrates that the patient has responded to therapy and predicts reliably a favorable outcome. In contrast, prolonged elevation of CRP values did not regularly predict a poor prognosis, since no less than 56 (69%) of the 81 patients with an elevated CRP still by week 6 recovered without complications.

Also the fall in the WBC count was significantly faster when a patient had an uncomplicated recovery of IE than when complications developed or death ensued. However, although elevated WBC counts were associated with death, normal WBC counts did not invariably predict a good prognosis. Thus, normalization of WBC count was less useful than normalization of CRP as a tool to monitor the outcome of patients with IE. There was a poor correlation between the levels of ESR and various characteristics of IE. It is of particular note that the changes of ESR during treatment and the development of endocarditis-related complications were not associated. Thus, ESR is not a useful marker for monitoring a patient's response to therapy in IE. This

may at least partly be due to the fact that ESR changes more slowly than the CRP and WBC count.

In the present study, patients with a high CRP value needed also cardiac surgery more often than those with a low CRP value. Unfortunately, the study design did not allow definition of any limits for the CRP value, which would predict a fatal outcome in case the operation is delayed. Probably, however, limits for CRP would not in themselves indicate mandatory surgery, since the decision to operate cannot be based on the levels of infection parameters only.

There are marked differences between countries in the use of CRP: it is frequently used in Europe, but rarely in the USA. This may be due the fact that according to conclusions of some studies and critical reviews, the CRP value alone cannot be used to differentiate between bacterial and viral infections, nor for instituting or withholding antimicrobial therapy on a patient's admission to hospital. (Young, Gleeson et al. 1991; Jaye and Waites 1997) However, there is general agreement in that once a firm diagnosis of a bacterial infection has been made, serial measurements of CRP are useful for monitoring a patient's response to antimicrobial therapy. (Young, Gleeson et al. 1991; Jaye and Waites 1997) The results of the present study indicate that this conclusion is valid also for patients with IE. In agreement with previous studies (Hogevik, Olaison et al. 1997; Olaison, Hogevik et al. 1997), the serum CRP value was here the most sensitive laboratory test to detect infection.

6.4. Broad-range bacterial PCR for etiological diagnosis of IE (IV)

In 1994 broad-range bacterial rDNA PCR combined with species identification by DNA sequencing was adopted as a routine diagnostic tool to examine valve tissue removed during cardiac surgery from patients treated at the Turku University Central Hospital for diagnosed or suspected IE. The first etiological diagnosis made by this new method involved *B. quintana* directly from excized valve tissue in a patient with culture-negative IE. The case was the first diagnosed *Bartonella* endocarditis in Finland. (Jalava, Kotilainen et al. 1995) This experience gave the impetus for a prospective clinical study, during which valve samples of 56 patients who had undergone surgery for diagnosed or suspected IE between 1994 and 2004 were analyzed using PCR. Most of the etiological agents identified by PCR from the affected valve tissue were common pathogens and had been identified preoperatively, based on blood cultures. However, the PCR approach was the only method to provide the etiological diagnosis for 4 patients, all of whom had received antimicrobial therapy before blood cultures were taken. Besides *B. quintana*, the other causative agents that were identified based on the presence of specific rDNA sequences from blood culture-negative IE patients were *Staph. aureus*, *Staph.* species and *Strep. bovis*. Thus, the results of the present study are in agreement with those of previous studies showing that the PCR-approach is useful especially in the following 2 clinical situations: 1) infections caused by bacteria with unusual growth requirements and 2) specimens taken during antimicrobial treatment leading to negative cultures from the valve tissue and blood. (Goldenberger, Kunzli et al. 1997; Rantakokko-Jalava, Nikkari et al. 2000; Kupila, Rantakokko-Jalava et al. 2003; Breitkopf, Hammel et al. 2005)

Bacterial DNA may persist during treatment in infected valves for long periods. (Lang, Watkin et al. 2004) In the present study the causative agent of IE was recognized by PCR from resected valve tissue for up to 58 days after start of parenteral antimicrobial treatment, whereas bacterial cultures of valve tissue became negative within only a few days. This finding provides further support to the contention that PCR may be particularly useful for establishing an etiological diagnosis to patients with blood culture-negative IE.

Long term persistence of bacterial DNA on heart valves during antimicrobial treatment has been observed also by other groups. In the series of IE patients reported by Podglajen et al. (Podglajen, Bellery et al. 2003), the mean duration of preoperative antimicrobial treatment was 25 days (range, 1 to 75 days) for the patients with PCR-positive valves. The persistence of bacterial DNA on heart valves observed early during the present study was initially a perplexing observation. Might not a positive PCR test from the valve tissue indicate inadequate treatment response? The association between a positive PCR test and an inadequate response to antimicrobial treatment cannot be established nor excluded, based on the findings of the present study.

It is of note that there are studies showing that bacterial DNA is detectable in the valve tissue even after the completion of antimicrobial therapy. In this respect, particularly interesting are the results of Rovery et al. (Rovery, Greub et al. 2005) showing that the PCR result is sometimes positive for years after an apparently successful treatment of IE. Based on these findings, the authors warn against using the PCR method as a tool to monitor treatment. At the present time, factors associated with the persistence of bacterial DNA in heart valves are unknown.

Of all 13 patients with definite IE who had PCR-negative valves in this study, antimicrobial treatment was considered inadequate in 8 (62%) patients. Thus, it is quite evident that a negative PCR test at the time of surgery does not mean that the patient has responded favorably to the given antimicrobial therapy.

Many authorities have suggested that molecular diagnostics should be included as a major criterion in the Duke diagnostic classification. (Li, Sexton et al. 2000; Millar, Moore et al. 2001; Bosshard, Kronenberg et al. 2003) The proposal is based on findings that a number of cases of possible IE can be classified as definite, if the results of the molecular tests are taken into account. One can assume that the PCR-based methods in the diagnostics of IE are especially useful in countries where culture-negative IE is commonly caused by fastidious and slow-growing bacteria, such as *C. burnetii* and *Bartonella* species. In the present study, inclusion of the PCR results would not have affected the classification of IE. For 4 patients with PCR-positive valves the diagnosis was postoperatively changed from possible IE to definite IE, but this was done on the basis of histological findings. For the most part, the concept of including molecular diagnostics into the classification schema may be considered as a sensible thing to do. It would certainly facilitate the etiological diagnosis of blood culture-negative IE.

6.5. In-hospital and 1-year outcome after IE (V)

Several previous studies from the 1990's and 2000's show that mortality of IE is still high: 10-24%. (Watanakunakorn and Burkert 1993; Netzer, Zollinger et al. 2000; Hoen, Alla et al. 2002) However, some authors have reported a decreasing mortality trend, attributed either to reduced operative mortality (Tornos, Olona et al. 1995) or more successful early valve surgery. (Hoen, Alla et al. 2002; Chu, Cabell et al. 2004) In previous studies, attempts have been made to identify various clinical and microbial factors which would predict either short-term or long-term mortality of IE. According to these studies, the outcome of IE seems to be associated with several clinical variables (age, underlying diseases, complications of IE), echocardiographic findings, laboratory parameters of inflammation, and the virulence of the causative microorganisms (Delahaye, Ecochard et al. 1995; Tornos, Olona et al. 1995; Cabell, Jollis et al. 2002; Netzer, Altwegg et al. 2002; Wallace, Walton et al. 2002; Hasbun, Vikram et al. 2003; Chu, Cabell et al. 2004; Thuny, Di Salvo et al. 2005), but the results from different hospitals have been somewhat conflicting.

Throughout the 1-year follow-up, the patients with *Strep. pneumoniae* IE had a significantly higher mortality rate than the other patients. In the antibiotic era, *Strep. pneumoniae* endocarditis has been considered an uncommon disease, with a constantly high mortality. A review of 197 adult patients with pneumococcal endocarditis described in the English literature between 1966 and 1996 showed that their overall mortality rate was 63%. (Aronin, Mukherjee et al. 1998) The high mortality rate of 46% in our patients with pneumococcal IE is in line with this finding, demonstrating the aggressive and destructive course of this disease.

It has been shown that *Staph. aureus* may be associated with a worse prognosis than other causative microorganisms (Roder, Wandall et al. 1999; Cabell, Jollis et al. 2002; Hasbun, Vikram et al. 2003; Miro, Anguera et al. 2005; Nadji, Remadi et al. 2005) – the death risk may be 1.5 fold over 1 year compared to the death risk from IE due to other pathogens. (Cabell, Jollis et al. 2002) Yet, in another study (Wallace, Walton et al. 2002), *Staph. aureus* was not associated with an adverse outcome. The authors assumed that this finding might have been due to the fact that among their patients with *Staph. aureus* IE, there was a high incidence of tricuspid valve involvement in which no deaths occurred. In the present study, 20 of the 75 episodes of *Staph. aureus* IE were in patients with IVDU, of whom 15 had tricuspid valve IE and survived. This may have contributed to the fact that although there was a tendency for a higher mortality in *Staph. aureus* IE as compared to the rest of the cases excluding *Strep. pneumoniae* IE, the association was significant only at 3 months.

A new finding in this study (V) was that high CRP values on admission were significant predictors of short-term and 1-year mortality. Patients who had CRP values ≥100 mg/l on admission had a hazard ratio for in-hospital death that was 2.9-fold compared to the patients with lower CRP values. The corresponding figure for 1-year mortality was 3.9-fold. No study has previously focused on the level of the first CRP value as a prognostic sign in IE. On the other hand, Wallace et al. (Wallace, Walton et al. 2002) have reported that in-hospital and 6-month mortalities are not affected by an

abnormal or normal CRP value within 48 hours of admission. These authors found that mortality was strongly associated with abnormal WBC counts or serum creatinine concentrations. In the present study, patients with an elevated WBC count on admission did not have an exceptionally poor outcome, but there was a tendency for higher mortality among the patients with elevated serum creatinine concentrations. However, the results of these 2 studies are not comparable, since the creatinine breakpoint concentration in study V was set at ≥100 µmol/, while the creatinine breakpoint used by Wallace et al. was ≥133 µmol/l. (Wallace, Walton et al. 2002)

The relation between survival and echocardiographic findings of IE is controversial. According to Hasbun et al. (Hasbun, Vikram et al. 2003), the presence of a vegetation was not associated with increased 6-month mortality of IE, and in another recent series of Chu (Chu, Cabell et al. 2004), echocardiographic findings were not predictive of in-hospital mortality. It is of note that in these 2 studies, the size and mobility of the vegetation were not analyzed. In contrast, many other studies have shown that certain echocardiographic findings are significantly associated with mortality. For example, in a prospective multicenter study, Thuny et al. found that vegetation length was a strong predictor of 1-year mortality. (Thuny, Di Salvo et al. 2005) In addition, Cabell et al. (Cabell, Pond et al. 2001) have shown that in patients with aortic or mitral valve endocarditis, the size of the vegetation was a predictor of mortality at 30 days and 1 year. Further, in right-sided IE among drug addicts, size of vegetation >20 mm was a major prognostic factor of in-hospital mortality. (Martin-Davila, Navas et al. 2005) In another study (Wallace, Walton et al. 2002), a visible vegetation on echocardiography influenced 6-month mortality significantly, but not in-hospital mortality. The results of the present study are in agreement with many of these findings, since at 3 and 6 months, and at 1 year, the mortality of patients with an echocardiographic vegetation was significantly higher than the mortality of patients with no vegetation. In the present study, a visible vegetation increased the death risk within 1 year 2.6-fold.

Data regarding the role of echocardiography in predicting embolic events has been conflicting. Recent studies suggest that vegetations, and especially certain characteristics of vegetations, are associated with a greater stroke rate. (Cabell, Pond et al. 2001; Thuny, Di Salvo et al. 2005) The results of study (V) are at variance, since a visible vegetation on echocardiography predicted only peripheral emboli, not cerebral emboli or other neurological complications. Unfortunately, the size and mobility of the vegetations were not recorded here.

Of the complications of IE, heart failure was most significantly associated with an adverse outcome during the index hospitalization and up to 1 year from admission. This is consistent with other studies which have found heart failure to be a major risk factor for mortality. (Siddiq, Missri et al. 1996; Hasbun, Vikram et al. 2003) Also consistent with other studies (Netzer, Zollinger et al. 2000), neurological complications and peripheral emboli predicted both in-hospital and 1-year mortality (V).

Mortality was somewhat higher among the patients in the present study who underwent surgery than for those treated conservatively. This finding was evidently due to more severe valvular disease in the surgically treated group of patients.

6.6. Changing epidemiology of IE (VI)

Considerable changes have occurred in many countries in the clinical pattern of IE over the past 20-30 years. The risk factors, causative microorganisms and the age of the patients with IE have changed. (Bayer 1993; Mylonakis and Calderwood 2001; Moreillon, Que et al. 2002) New risk factors, such as IVDU, long term hemodialysis, and nosocomial disease have emerged over the years. (Moreillon and Que 2004) However, there are some studies in which such changes have not been observed. (Tornos, Olona et al. 1995; Netzer, Zollinger et al. 2000; Tleyjeh, Steckelberg et al. 2005) The purpose of the present study was to assess the changes, if any, in the clinical presentation of endocarditis among patients treated in a Finnish teaching hospital during a period of 25 years.

This study shows that there has been a significant increase of IVDU-associated episodes of IE after 1996. These episodes comprised overall only 8% of the episodes, but 20% of the episodes between 2000 and 2004. Consistent with previous studies, (Cabell, Jollis et al. 2002) chronic dialysis turned out to be a progressively more important risk factor for IE also in this study, although the ultimate number of the disease episodes was small.

There was no major change in the spectrum of predisposing heart diseases between the different time periods. The most common predisposing cardiac condition was acquired valvular disease, followed by a prosthetic heart valve. Only 10% of our patients had mitral valve prolapse, although it is now thought to be a major cardiac abnormality encountered with IE. (Steckelberg and Wilson 1993; Mylonakis and Calderwood 2001) Several earlier papers from the 2000's have reported an increase in the proportion of IE among patients with no predisposing heart disease. (Nissen, Nielsen et al. 1992; Hoen, Alla et al. 2002) In the present study there were such episodes in 26% in the years 1980-1984 and 39% in the years 2000-2004, but the change was not statistically significant.

Aortic valve was overall the predominant site of infection. However, the proportions of aortic valve and prosthetic valve IE decreased with time, while the proportions of mitral and tricuspid valve IE increased. This change was not seen in patients with no IVDU.

The mortality of IE during 3 months after the diagnosis was 13%, and was similar throughout the entire study period from 1980 to 2004. This is in agreement with previous studies from the 1990's and 2000's that have reported in-hospital mortality rates of 10% to 24%. (Watanakunakorn and Burkert 1993; Delahaye, Goulet et al. 1995; Sandre and Shafran 1996; Netzer, Zollinger et al. 2000; Fefer, Raveh et al. 2002) During the whole study period, mortality remained slightly higher among the surgically treated patients at our hospital, and there was no change in the proportion of patients requiring surgery. Similarly, the incidence of neurological manifestations, peripheral emboli, and heart failure as complications of IE did not change. Only the incidence of lung emboli increased, but these complications occurred mainly in the patients with IVDU.

Today, IE is considered mainly a disease of old people. (Alestig, Hogevik et al. 2000) This concept is supported by the results of the present study showing a significant increase in the mean age of the patients between the first and last 5-year period (from 47 to 55 years). The increase was more conspicuous among the patients with no IVDU, whose mean age was 62 years during the last period.

In many recent patient populations, *Staph. aureus* has surpassed the viridans streptococci as the most common agent causing IE. (Cabell, Jollis et al. 2002; Loupa, Mavroidi et al. 2004; Fowler, Miro et al. 2005; Tornos, Iung et al. 2005) The same trend was seen in the episodes of IE analyzed here, as viridans streptococci were the predominant pathogens during 1980-1994, but after that the proportion of *Staph. aureus* increased significantly and it became the most common. Again, this increase was mainly due to the emergence of IVDU-associated endocarditis, caused by *Staph. aureus*. If the patients with IVDU were excluded from the analysis, the proportions of viridans streptococci and *Staph. aureus* would be practically identical during the last 5-year period (22% and 21%).

Collectively, the findings presented in this study indicate that most of the changes regarding the agents that cause IE, the valves that are affected by IE and the complications that arise from IE were associated with the emergence of IVDU. In this respect, the present study corroborates some previous findings according to which the clinical presentation and course of IE have not changed during the recent decades. (Tornos, Olona et al. 1995; Netzer, Zollinger et al. 2000; Tleyjeh, Steckelberg et al. 2005) In contrast, several other recent studies from European countries have reported important changes in disease characteristics and epidemiology of IE. (Hoen, Alla et al. 2002; Loupa, Mavroidi et al. 2004)

7. SUMMARY AND CONCLUSIONS

IE is difficult to diagnose and treat. Despite major diagnostic and therapeutic advances, the morbidity and mortality associated with IE remain high. Although the incidence of IE has not changed during the past 20-30 years, considerable changes have occurred in the clinical pattern of the disease in many countries. This study was made to evaluate the clinical presentation and outcome of the patients with IE treated in a Finnish teaching hospital during a period of 25 years.

This study is one of the first to validate the diagnostic criteria of the Duke classification in a clinical setting. The Duke criteria turned out to be more sensitive than the older, von Reyn criteria. Among the histopathologically proven episodes of IE, the sensitivity of the Duke criteria was 72%, and none of the pathologically proven cases, whether native or prosthetic valve disease, were rejected by the Duke clinical criteria. None of the patients included in this part of the study were drug addicts. Thus, these results confirm the validity of the Duke criteria also in a patient population with no IVDU.

Many previous studies have endeavored to find means to reduce neurological complications in patients with IE. In this work, patients with IE-associated neurological complications were carefully assessed and compared with endocarditis patients with no neurological symptoms. Particular attention was paid on assessing the impact of cardiac surgery and potential risk factors for complications on the outcome of the patients with IE. Neurological complications were identified in 25% of episodes; an embolic event was the most frequent manifestation. In the majority of episodes, the neurological manifestation emerged before antimicrobial treatment was started, being the first sign of IE in 47% of episodes. Only one recurrent cerebral embolization was observed during antimicrobial treatment. Neurological complications were significantly associated with death during the acute phase of IE. These data reinforce the concept that rapid diagnosis and early start of antimicrobial therapy may still be the most effective means to prevent neurological complications. Diagnostic alertness is crucial for the prognosis of patients with endocarditis.

In this study, extensive statistical analyses were used to assess the diagnostic usefulness of serial CRP, ESR and WBC determinations for monitoring patients' responses to therapy. High CRP and WBC counts were associated with a complicated course of IE and death. A rapid normalization of serum CRP concentration or WBC count predicted uncomplicated recovery, while ESR was not useful in this respect. Normalization of CRP during treatment was associated with an invariably good prognosis of IE. Collectively, these data indicate that the normalization of CRP predicts a favorable late outcome (surgery, death) of IE. Also WBC determination proved useful for assessment of patients with IE, but the value of ESR was negligible.

The value of direct amplification of rRNA genes from surgically removed valve tissue for etiological diagnosis of IE was assessed in patients undergoing surgery for IE. Most etiological agents recognized by PCR of affected valve tissue were common pathogens

identified already preoperatively from blood cultures. PCR was the only method to give an etiological diagnosis in 4 additional patients with culture-negative IE (2 *Staphylococcus* species, 1 *Strep. bovis*, 1 *B. quintana*), all of whom had received antimicrobials before blood cultures were taken. Bacterial DNA persisted during treatment in the infected valves for long periods, for up to 58 days. These results support the concept that broad-range bacterial rDNA PCR followed by sequencing from surgically removed valve tissue is valuable for etiological diagnostics of blood culture-negative IE. The PCR approach was useful, when the causative agent of IE was fastidious or when the specimen was taken during antimicrobial treatment. In a routine clinical setting, it is not necessary to use PCR to examine valve tissue from patients, whose preoperative blood cultures have yielded an etiological diagnosis of IE. The implications of the persistence of nucleic acid on the affected heart valves are not known but merit further study.

Previous studies on the prognosis of IE have given somewhat conflicting results. Here, the aim was to define the factors predicting the outcome in patients treated in a Finnish teaching hospital. Some of the factors (e.g. heart failure, neurological complications, peripheral emboli) that predict a poor prognosis and need for surgery were the same as in previous studies, while some other previously established poor prognostic factors (diabetes, elevated WBC counts) did not have a prognostic influence in our patient population. A new finding was that a high CRP value on admission predicts short-term and 1-year mortality.

The clinical characteristics of the patients treated in a Finnish teaching hospital during the past 25 years were also evaluated. The purpose was to assess whether changes often reported as having occurred among patients that present with IE are also manifested in our patients. The emergence of IVDU-associated episodes of IE was the main change in the clinical presentation of IE over the years. A significant increase of these episodes after 1996 explained all changes regarding causative agents, affected valves, and complications. Chronic dialysis for renal failure is an underlying condition that also became more important with time. Except for a more advanced age, the clinical presentation and outcome of IE patients with no IVDU were substantially unchanged throughout 25 years of observation.

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