Infective Endocarditis at Autopsy

A Review of Pathologic Manifestations and Clinical Correlates

Manuel L. Fernández Guerrero, MD, Beatriz Álvarez, MD, Félix Manzarbeitia, MD, and Guadalupe Renedo, MD

Abstract: The frequency of autopsies appears to be declining, and the usefulness has been challenged. We reviewed cases of autopsied active infective endocarditis (IE) during 2 periods based on the availability of high-tech 2-dimensional echocardiograms: Period 1 (P1) included 40 cases studied from 1970 to 1985, and Period 2 (P2) included 28 cases seen from 1986 to 2008—that is, before and after the introduction of echocardiograms in our institution. We conducted the study to reassess the pathology of IE and to determine how frequently diagnosis is not made during life.

The age of patients increased 10 years on average between the 2 periods, and comorbidities were significantly more frequent in P2. While the frequency of rheumatic valve disease and prosthetic valve endocarditis (PVE) decreased, degenerative valve disease increased. Isolated mitral or aortic valve IE was most common. Right-sided IE was observed in patients with *Staphylococcus aureus* bacteremia from infected venous lines. In most cases IE involved only the cusps of cardiac valves. "Virulent" microorganisms caused ulcerations, rupture, and perforation of the cusps and necrosis of chordae tendiniae and perivalvular apparatus. In PVE the lesions were located behind the site of attachment, and vegetations were seen on the sewing ring in both metallic and biologic prostheses. Infection spread to adjacent structures and myocardium with ring abscess observed in 88% of cases. Prosthetic detachment causing valve regurgitation was associated with abscesses in 76% of cases; these patients developed persistent sepsis and severe cardiac failure. Obstruction occurred in patients with PVE of the mitral valve. Acute purulent pericarditis was observed in 22% of cases, mainly in patients with aortic valve IE and myocardial abscesses.

Gross infarcts were seen in 63% of cases but were asymptomatic in most instances. The spleen, kidneys, and mesentery were the sites most frequently involved. Myocardial infarctions were found in less than 10% of cases. Abscesses were also frequently found and were a common source of persistent fever and bacteremia. Glomerulonephritis was more common in the first period. Brain pathology consisted of ischemic and hemorrhagic infarcts and abscesses. Cerebral bleeding was more frequent in patients with PVE on anticoagulant therapy. Neutrophilic meningitis was observed in *S. aureus* IE.

Diagnosis of IE was not made during life in 14 (35%) cases during P1 and 12 (42.8%) cases in P2. Overall, diagnosis was missed until autopsy in 38.2% of cases. IE was hospital acquired in 28 instances. While a clinical diagnosis was made in all but 4 cases of early-onset PVE (23.5%), the diagnosis was not made during life in 22 of 51 patients with native-valve IE (43.1%). Of these 22 patients, IE was hospital acquired in 11 (50%). The absence of fever, cardiac murmurs, and many of the typical stigmata of endocarditis may have led to the diagnosis being overlooked clinically.

Brain bleeding, cardiac failure and less frequently acute myocardial infarct were the most common causes of death.

IE continues to be missed frequently until autopsy. Postmortem examination is an important tool for evaluating the quality of care, and for guiding teaching and research related to cardiovascular infections.

(*Medicine* 2012;91: 152–164)

Abbreviations: CT = computed tomography, IE = infective endocarditis, MRI = magnetic resonance imaging, P1 = Period 1, P2 = Period 2, PVE = prosthetic valve endocarditis, TTE = transthoracic echocardiogram, TEE = transesophageal echocardiogram.

INTRODUCTION

In spite of the established value and the compelling scientific evidence in favor of autopsy, its usefulness has been challenged, and the frequency of autopsies in general and in university hospitals appears to be declining.[31,61] Several reasons have been suggested to explain this trend: cost, reluctance to ask the family for permission to carry out the autopsy, doubt about the value of the procedure, and confidence in newer diagnostic techniques.

Before the introduction of echocardiography as a diagnostic tool in infective endocarditis (IE), definitive diagnosis rested on visualization of cardiac vegetations during surgery or autopsy.[79] Now the echocardiogram, particularly the transesophageal echocardiogram (TEE), allows identification of valve vegetations, and direct visualization is no longer required for definitive clinical diagnosis of IE.[41] However, discrepancies between clinical and autopsy diagnoses persist in spite of progress in medical skills and technology.[8,33]

The diagnosis of IE is not an easy matter. Manifestations are not always typical, and many are nonspecific and similar to those found in many other systemic diseases.[45,47,49] In addition, IE frequently occurs in elderly patients with comorbidities, and manifestations of endocarditis can be wrongly attributed to the underlying disease.[14,73,84] Hence, the diagnosis of IE is often not considered and may be missed until autopsy. At the present time, when IE frequently occurs as a nosocomial infection during admission for another condition, missed diagnoses may be even more frequent.[10,22–24,28] Of note, in a 2007 series of autopsies from a specialized cardiology hospital, the clinical diagnosis of IE was not made during life in 27% of cases.[64]

Since the publication of large autopsy series in the early antimicrobial era,[15,21,34,53] we have witnessed several changes in the epidemiology, microbiology, diagnostics, and therapeutics of IE.[6,10,14,30,45,47,49,70] Few recent studies have focused on pathologic manifestations of endocarditis or have compared clinical and autopsy diagnoses of IE in a general hospital.[64]

From the Division of Infectious Diseases (Department of Medicine) and Surgical Pathology, Instituto de Investigaciones Sanitarias Fundación Jiménez Díaz, Universidad Autónoma de Madrid, Madrid, Spain.
The authors have no funding or conflicts of interest to disclose.
All figures can be viewed in color online at http://www.md-journal.com.
Reprints: Manuel L. Fernández Guerrero, MD, Fundación Jiménez Díaz. Avda. Reyes Católicos, 2; 28040 Madrid, Spain (e-mail: mlfernandez@fjd.es).

ISSN: 0025-7974
DOI: 10.1097/MD.0b013e31825631ea

Minimally invasive autopsy, a combination of computed tomography (CT) with magnetic resonance imaging (MRI) followed by ultrasonography-guided biopsy that has been proposed as an alternative to autopsy, failed to demonstrate IE in 1 study.[85]

In the current study we reassessed the role of postmortem examination as a source of knowledge in IE, based on the idea that understanding the morphologic changes caused by the infection provides the basis for diagnosis and therapy. Specifically we studied how frequently the diagnosis was not made during life, and how frequently autopsy showed unexpected findings compared to the clinical diagnosis and clinical cause of death. We also provide here a review of the general morphology of IE with an update of clinical correlates.

METHODS

We conducted a retrospective review of patients with active IE in whom autopsy was performed in a tertiary care, university-affiliated hospital serving a population of 350,000 people in downtown Madrid, Spain.

The clinical diagnosis of IE was made following the criteria proposed by von Reyn et al[79] during the first period of the study and the Duke modified criteria[41] after the first period. (Study periods are defined below.) Autopsy diagnosis was made on the basis of macroscopic and microscopic examination. Specifically, pathologic diagnosis of IE required the presence of vegetations in cardiac valves or mural endocardium composed by fibrin, platelets, leukocytes, or histiocytes. Because patients were commonly treated with antimicrobials, the presence of microorganisms on Gram stain of vegetations was not required for inclusion. Only cases of active endocarditis—defined by positive blood cultures within 2 weeks before death, or microorganisms identified in Gram stain of vegetations, or truly endocardial pathogens isolated in tissue cultures—were included in the analysis. Because of the similarities with IE, 2 cases of infective aortitis of the ascending thoracic aorta were also assessed.

The complete autopsy charts and the clinical and laboratory records were reviewed by 2 clinicians and 1 pathologist. We looked at the clinical manifestations, methods for diagnosis, alternative diagnoses, causative agents, complications, laboratory findings, medical treatment, and pathologic findings. Postmortem examination was performed following the recommendations of the College of American Pathologists.[37] When permission was granted, the brain was also examined.

Cases were classified into 2 different periods of time based on the availability of 2-dimensional echocardiograms in our institution: Period 1 (P1) from 1970 to 1985, before the introduction of high-tech 2-dimensional echocardiograms; and Period 2 (P2) from 1986 to 2008, when both transthoracic echocardiogram (TTE) and later TEE were available and routinely used in the diagnosis of IE in our hospital.

Hospital-acquired IE was defined as endocarditis developing ≥72 hours after admission in association with a hospital-based procedure or during another hospitalization within the preceding 8 weeks.[22] Prosthetic valve endocarditis (PVE) was defined as early onset when it developed within the first year after valve replacement.[42,65]

Statistical Analysis

SPSS v. 11.0 (SPSS Inc., Chicago, IL) was used for the statistical analysis. Continuous variables were expressed as mean (range). Discrete variables were expressed as percentages. Associations were tested by chi-square test or the Fisher exact test when samples were small. Differences between groups were considered significant at p value < 0.05.

RESULTS

We discuss here the results of the study, and present pertinent case reports to illustrate the findings.

The number of autopsies performed in our institution showed a continuous decline since the 1990s despite a significant increase in the number of admissions to the hospital. The autopsy rate declined from 14.8% and 14.6% of all deaths in 1975 and 1985, respectively, to 5.73% in 1994, 4.9% in 2000, and 2.29% in 2008. Frequency of IE at autopsy ranged from 0.5% in 1971 to 3.9% in 1984 (average, 1.5% in the entire period).

In P1, January 1970 through December 2008, 750 patients received a diagnosis of IE at Fundación Jiménez Díaz, Madrid. From 1970 to 1985, 227 cases were seen, of whom 86 (37.8%) died. Postmortem examination was performed in 40 (46.5%) of these deceased patients. In P2, from 1986 to 2008, 523 cases of IE were seen, of whom 116 (22.1%) died. Autopsy was performed in 28 (24.1%) cases of IE during this period. Hence, 68 autopsied patients were assessed and compose the basis for this study.

The mean age increased from 46.6 years in P1 to 57.6 years in P2. No differences were observed in the distribution by sex. One or more comorbid condition was found in 11 (27.5%) cases studied in P1. In comparison, 17 (60.7%) cases in P2 had 1 or more comorbid condition ($p < 0.01$). Solid neoplasms ($n = 4$ and $n = 5$ in P1 and P2, respectively), chronic renal failure on hemodialysis ($n = 2$ and $n = 5$, respectively), cirrhosis of the liver ($n = 2$ and $n = 6$, respectively), and other miscellaneous diseases such as diabetes mellitus, atherosclerosis and its complications, systemic lupus erythematosus, rheumatic polymyalgia, or polyneuropathy were the most common underlying disorders.

A predisposing valve disorder was observed in 72.5% and 75% of cases in P1 and P2, respectively. While the frequency of rheumatic valve disease and PVE decreased from P1 to P2 (10/25% vs. 4/14.2% and 12/30% vs. 5/17.8%, respectively), the frequency of degenerative valve disease increased (5/12.5% vs. 9/32.1%; $p < 0.05$). All cases of PVE developed within 1 year after valve replacement and were considered early-onset PVE. Other less frequent underlying cardiac diseases were congenital cardiomyopathy and myxoid valve disease. A preexistent cardiac condition could not be determined in 11/17.5% and 7/25% of cases of P1 and P2, respectively (p not significant).

IE was hospital acquired in 28 (41%) instances. Eighteen cases occurred during P1 (12 early PVE, 5 associated with infected central venous lines, and 1 in a patient on hemodialysis), and 10 occurred during P2 (5 early PVE, 2 in patients on hemodialysis, 2 due to infected central venous catheters, and another 1 associated with urologic instrumentation).

The microorganisms isolated from blood cultures and/or valve vegetations are shown in Table 1. *Staphylococcus aureus,* coagulase-negative staphylococci, and enterococci were the most common etiologic agents. As expected, less invasive bacteria such as *Streptococcus viridans* were less frequently found in this series of autopsies. Gram-negative bacilli, which in the early days of cardiac surgery were important causes of early-onset PVE in our institution, were not found in P2.

Isolated mitral or aortic valve and combined mitral and aortic valves were the most common sites of IE within the heart (Table 2). In 5 autopsies, mural endocarditis of the right atrium and eustachian valve was observed. In addition, isolated left atrial endocarditis was noted in 1 autopsied patient. We note that the clinical diagnosis of most of these cases of mural endocarditis

TABLE 1. Microbial Etiology of Infectious Endocarditis in Autopsies of 68 Patients

Etiology	Time Period No. (%) Period 1 (1970–1985) (n = 40)	Period 2 (1986–2008) (n = 28)
Staphylococcus aureus	10 (25)	9 (32)
Coagulase-negative staphylococci	4 (10)	4 (14)
Enterococci	6 (15)	5 (18)
Streptococcus viridans	3 (7)	2 (7)
Other Gram-positive bacteria*	4 (10)	4 (14)
Gram-negative bacilli†	6 (15)	0
Fungi‡	1 (2.5)	3 (11)
Unknown	6 (15)	1 (3.5)

*Beta-hemolytic streptococci.

†*Pseudomonas aeruginosa, Serratia marcescens, Burkholderia cepacia*.

‡*Candida albicans, Aspergillus fumigatus*.

was not made during life, and all corresponded to patients with *S. aureus* bacteremia from an infected central venous catheter.

The following history illustrates the complexity of clinical diagnosis of 1 of these cases.

Case 1

A 73-year-old man with colon cancer and metastases to the liver was admitted because of hematemesis. A central venous line was inserted for administration of blood and fluids. Five days later he developed fever, and *S. aureus* was isolated from blood cultures. The catheter was withdrawn and treatment with intravenous cloxacillin was started. Fever rapidly subsided, and antimicrobial therapy was discontinued after 12 days. Fever and staphylococcal bacteremia relapsed. No murmurs were heard, and TTE did not show valve abnormalities. Antimicrobial therapy was reinitiated, but the patient followed a downhill course with gastric bleeding, shock, and respiratory failure. Postmortem examination showed extensive endocarditis of the tricuspid valve, eustachian valve, and right atrium (Figure 1). Pulmonary emboli and lung infarcts were also observed.

TABLE 2. Anatomic Site Involved in Infective Endocarditis

Site	Time Period No. (%) Period 1 (1970–1985) (n = 40)	Period 2 (1986–2008) (n = 28)
Single valve		
Mitral	13 (32.5)	11 (39)
Aortic	10 (25)	9 (32)
Tricuspid	2 (5)	
Multiple sites		
Mitral & aortic valves	8 (20)	5 (18)
Mitral & tricuspid valves	1	0
Aortic & tricuspid valves	1	1
Mitral & aortic & tricuspid valves	1	0
Mural	5 (12.5)*	1
Ascending aorta	1	1

*Isolated right atrium or associated with tricuspid valve involvement (n = 4); isolated left atrium (n = 1).

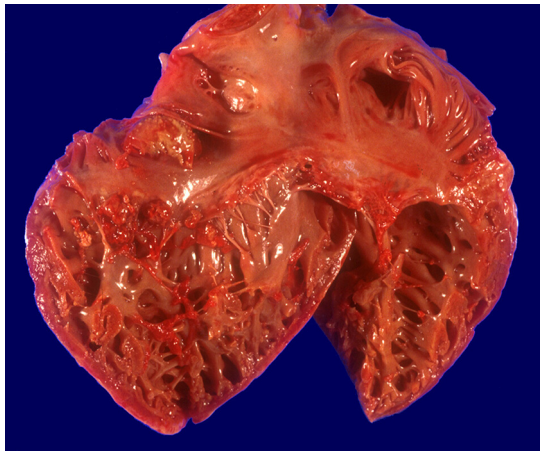

FIGURE 1. Case 1. Tricuspid valve endocarditis due to *S. aureus*. Note vegetations on cusps, the chordae tendiniae and a large vegetative mass on the mural atrial endocardium involving the eustachian valve. [This figure can be viewed in color online at http://www.md-journal.com.]

Cardiac Pathology

A summary of cardiac pathology is shown in Table 3. Cardiac weight ranged from 363 g to 810 g (mean, 494 g). In most cases endocarditis involved only the cusps of cardiac valves. Vegetations measured from 3 mm to 42 mm in greater diameter and were always located on the atrial aspect of the mitral valve and on the ventricular aspect of the semilunar

TABLE 3. Cardiac Pathology

Involvement	Time Period No. (%) Period 1 (1970–1985) (n = 40)	Period 2 (1986–2008) (n = 28)
Only cusps	17 (42.5)	18 (64.2)
Ruptured chords	2	3 (10.7)
McCallum patches	1	4 (9.5)
Ring abscess	12 (30)	8 (28.5)
PVE	10	5
Aortic valve	6	2
Mitral valve	4	3
Native valve	2	0
Aortic valve	1	1
Dehiscence (only PVE)	9 (75)	4 (80)
Valve obstruction	4 (10)	1
PVE	3 (75)	1 (100)
Native valve	0	1
Pericarditis	6 (15)	9 (32)
Focal myocarditis	5 (12.5)	3 (10.7)
Intracardiac fistulae	2	1
Myocardial infarction	4 (10)	2 (7.1)

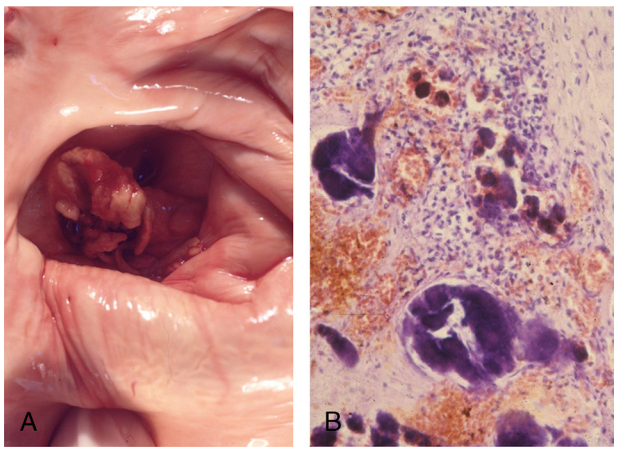

FIGURE 2. **A**. Vegetation measuring 32 × 41 mm on the mitral valve. **B**. Microscopic view (original magnification × 100). Gram stain showing abundant microcolonies of Gram-positive bacteria. Cultures yielded *S. aureus*. [This figure can be viewed in color online at http://www.md-journal.com.]

valves. The largest vegetations were observed in infections caused by *S. aureus* (Figure 2A). When not treated with antimicrobials, vegetations were composed of a matrix of fibrin and platelets with scarce macrophages and bacterial microcolonies, although in staphylococcal infections infiltrates by polymorphonuclear cells were commonly observed (Figure 2B).

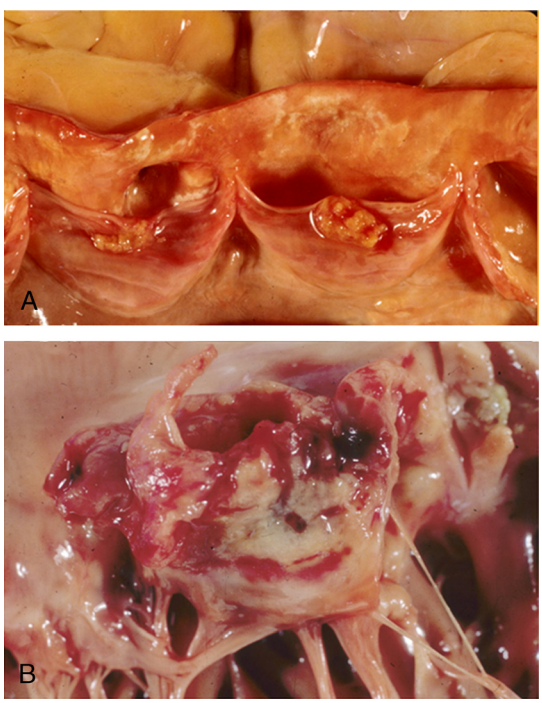

FIGURE 3. Different severity of valve damage. **A**. Small vegetations located on the line of closure of the ventricular surface of the cusps of aortic valve in a case of enterococcal endocarditis. **B**. Severe mitral valve damage with hemorrhage, ulceration, and rupture of the cusps and chordae tendiniae in a case of endocarditis caused by *S. aureus*. [This figure can be viewed in color online at http://www.md-journal.com.]

The shape of vegetations was polypoid, cauliflower-like or verrucous, and the surface rough or granular.

Generally speaking, small vegetations not producing significant damage of the cusps were not associated with severe hemodynamic disturbance (Figure 3A). On the other hand, more invasive infections causing ulcerations, rupture and perforation of the cusps, and necrosis of chordae tendiniae and perivalvular apparatus were generally associated with greater degrees of heart failure (Figure 3B). Ruptured chordae tendiniae were seen exclusively in cases of mitral endocarditis caused by *S. aureus*. Extension of infection into the surrounding myocardium with abscess formation was observed in 5 cases of aortic native-valve endocarditis. Satellite left atrial vegetations due to regurgitant, high-velocity jet stream (McCallum patches) were observed in a few cases of mitral endocarditis (Figure 4).

Pathology of PVE

Seventeen prosthetic valves were assessed: 12 during P1 (8 metallic and 4 porcine valves) and 5 during P2 (all metallic valves). Rigid-frame prosthetic valves, such as the Björk-Shiley, Medtronic-Hall, and Hall-Kaster and Hancock porcine bioprosthetic valves, were most frequently used in our institution during both periods.

In each case, infection was located behind the site of attachment, and vegetations were seen on the sewing ring both in metallic and in biologic prostheses (Figure 5A). Frequently, infection spread to adjacent structures and surrounding myocardium with abscess formation. Ring abscess was observed in 15 of 17 (88%) cases, without differences between aortic and mitral valve endocarditis or metallic and biologic prostheses. Ring abscess involved the entire annulus in 3 and only a portion of the annulus in another 12 (Figure 5B). Three patients with aortic valve endocarditis and myocardial abscess extending into the interventricular septum presented with atrioventricular conduction disturbances.

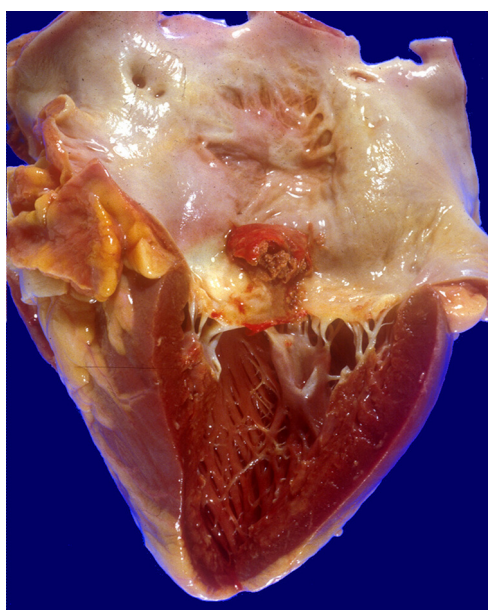

FIGURE 4. McCallum patches on the atrial surface due to the erosive action of high-velocity regurgitant flow in a case of acute mitral insufficiency due to *S. aureus* endocarditis. [This figure can be viewed in color online at http://www.md-journal.com.]

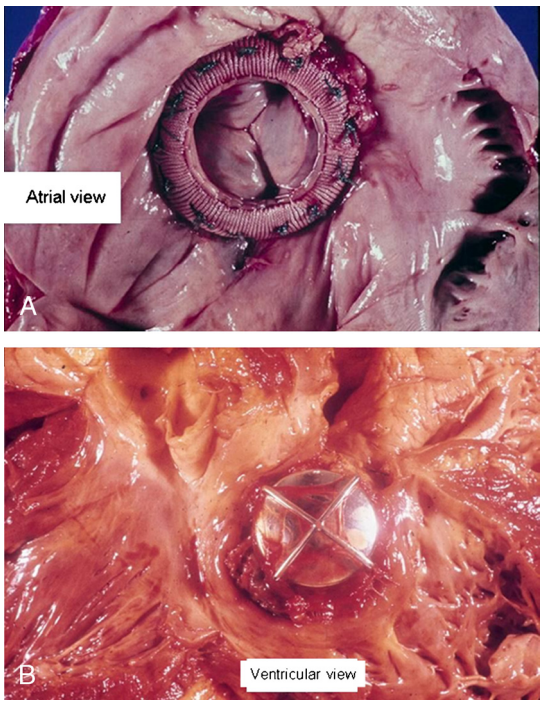

FIGURE 5. A. Hancock porcine bioprosthesis. Note vegetations on the sewing ring, while porcine cups appear free of infection. **B**. PVE occurring on a mitral metallic valve. Note the infective process surrounding the entire sewing ring and annulus. [This figure can be viewed in color online at http://www.md-journal.com.]

Intracardiac fistulae were observed in 2 cases of aortic PVE caused by *S. aureus* and *Streptococcus viridans* (Figure 6). Ring abscesses burrowed into adjacent structures through the atrial septum into the right atrium or through the interventricular septum into the right ventricle. These patients developed persisting sepsis and severe cardiac failure and died despite antimicrobial therapy.

Prosthetic detachment causing severe regurgitation was associated with abscesses of the sewing ring and was observed in 76.4% of cases. Valve obstruction was found in 5 (7.3%) cases in this series. Complete or partial prosthetic obstruction by vegetative material occurred in 4 of 7 patients with PVE of the mitral valve.

Case 2

A 62-year-old man with mitral stenosis had a valve replacement with a metallic Björk-Shiley valve. Two weeks later he was readmitted with fever and shortness of breath. No murmurs were heard, and peripheral stigmata of IE were not seen. Blood cultures were negative, and he was started on antimicrobial therapy with vancomycin and gentamicin. He remained febrile and developed refractory cardiac failure and shock, and died shortly after admission. At autopsy, mitral endocarditis caused by coagulase-negative staphylococci was found. The prosthesis was almost completely obstructed by vegetative material (Figure 7).

Acute purulent pericarditis was observed in 22% of cases, mainly in persons with aortic valve endocarditis and myocardial abscesses caused by virulent microorganisms such as *S. aureus* or *Pseudomonas aeruginosa*. Pericarditis was associated with persistent fever in most patients. Chest pain or other symptoms associated with pericarditis were not observed. However, pericardial effusion was observed by echocardiography when available.

Focal myocarditis was a microscopic finding in 12.5% and 10.7% of cases in P1 and P2, respectively, but its frequency was probably underestimated because multiple histologic sections were not routinely examined. The lesions consisted of scattered infiltrates of mononuclear cells with focal and discrete necrosis of myocytes (Bracht-Wächter bodies). Myocarditis did not seem to result in cardiac failure in patients in whom it was found.

Myocardial infarcts were observed in ≤10% of cases in both periods. Although not commonly found, acute myocardial infarct was always symptomatic, and was the cause of death in at least 1 case. Myocardial infarcts contributed to mortality in another 5 patients by causing worsening cardiac failure or precluding cardiac surgery.

Systemic Pathology

The systemic pathology consisted of visceral infarcts and abscesses and was particularly common and florid in cases of left-sided endocarditis (Table 4). Gross infarcts were seen 43 (63.2%)

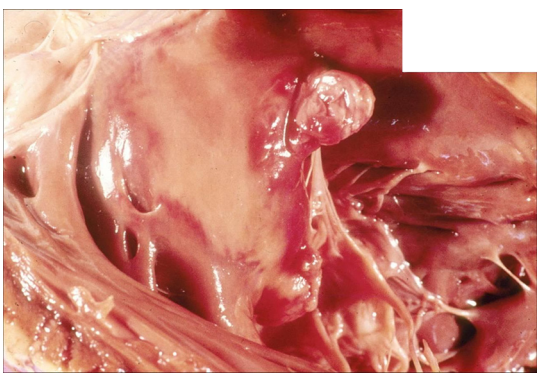

FIGURE 6. Intracardiac fistulae due to aortic PVE due to *Streptococcus mitior*. The ring abscess burrowed into adjacent structures through the ventricular septum into the right ventricle, producing a sinus tract covered by a large vegetative mass. The patient developed unremitting fever and refractory heart failure. [This figure can be viewed in color online at http://www.md-journal.com.]

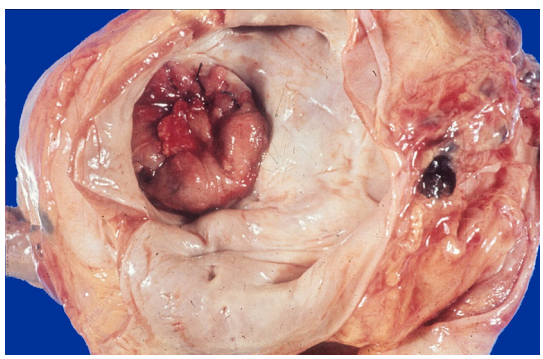

FIGURE 7. Case 2. Mitral valve obstruction caused by massive vegetations in a case of early-onset PVE caused by coagulase-negative staphylococci. The patient presented with heart failure without cardiac murmurs, and the diagnosis was missed until autopsy. [This figure can be viewed in color online at http://www.md-journal.com.]

TABLE 4. Systemic Pathology

Feature	Time Period No. (%)	
	Period 1 (1970–1985) (n = 40)	**Period 2 (1986–2008) (n = 28)**
Infarcts		
Spleen	14 (39)	8 (29)
Kidneys	11 (30)	10 (36)
Lungs	6 (17)	
Mesentery	3 (7.5)	1 (3.6)
Abscess		
Kidneys	7 (19)	5 (18)
Lungs	5 (14)	2 (7)
Spleen	2	3 (11)
Liver	2	1 (3.6)
Septic spleen	12 (30)	6 (21.4)
Arterial emboli	4 (10)	2 (7)
Glomerulonephritis	6 (15)	2 (7)
Mycotic aneurysms	3 (7.5)	2 (7)

autopsied patients. The spleen, kidneys, and mesentery were the sites most frequently involved. Lung emboli and infarcts were exclusively observed in cases of right-sided endocarditis.

A large, congestive, friable, septic spleen that was easily broken during extraction of the viscera was commonly observed. The weight of the spleen ranged from 50 g to 1050 g. While most splenic and renal infarcts were clinically silent, on occasion patients developed pain and hematuria.

Case 3

A 69-year-old man with cancer of the urinary bladder developed fever and *Enterococcus faecalis* bacteremia. A diastolic aortic murmur was heard. Antimicrobial treatment with ampicillin plus gentamicin was started. TTE showed aortic valve vegetations measuring 12 mm in diameter and mild aortic insufficiency. Forty hours after admission he developed pleuritic pain in the left flank that radiated to the shoulder. Chest X-ray films showed a mild pleural effusion in the left lung. Cardiac surgery was not considered. The patient's clinical condition was deteriorating, and he had acute lumbar pain followed by hematuria. Finally he developed severe aortic insufficiency with acute heart failure and died. At autopsy, aortic endocarditis with perforation and rupture of the cusps and extensive infarcts in the spleen and kidneys were seen (Figure 8).

Abscesses were frequently found in left-sided endocarditis and involved the kidneys, spleen, and liver. Lung abscesses were observed in cases of both right-sided and left-sided endocarditis. Abscesses were a common cause of persistent fever and bacteremia.

Case 4

A 71-year-old woman with diabetes mellitus was admitted because of hyperglycemic hyperosmolar coma. A central venous line was inserted and therapy with insulin and fluids was immediately started. General and metabolic conditions improved but she developed *S. aureus* bacteremia. The central venous line was removed and therapy with cefazolin was given. Fever persisted and in the following days a systolic murmur of mitral insufficiency was noted. Bacteremia subsided but spiking fever persisted despite antimicrobial therapy. On the morning of the 19th hospital day the patient fainted and became drowsy. A facial and left hemiparesis was observed. She died 48 hours later. At autopsy, mitral endocarditis and a large abscess in the spleen were observed.

Emboli of large arteries (iliac, subclavian, femoral) and mycotic aneurysms (ascending aorta, femoral and cerebral arteries) were other less frequent findings in the current series.

One patient with coarctation of the aorta had *S. aureus* aortitis leading to aortic rupture and sudden death. The following case report features a patient who developed suture-line aortitis after cardiac surgery.

Case 5

A 63-year-old diabetic man was admitted because of fever and chest pain. Five months before, coronary artery bypass grafting had been performed for severe 3-vessel atherosclerotic disease. On examination Janeway spots were observed in the pads of the fingers of the left hand. No murmurs were heard, and blood cultures were negative. TEE did not show valve vegetations but did demonstrate widening of the ascending aorta. A CT scan showed a mycotic aneurysm of ascending aorta and aortic arch. Treatment with vancomycin, gentamicin, and amphotericin B was started but the patient suddenly died. At autopsy, a

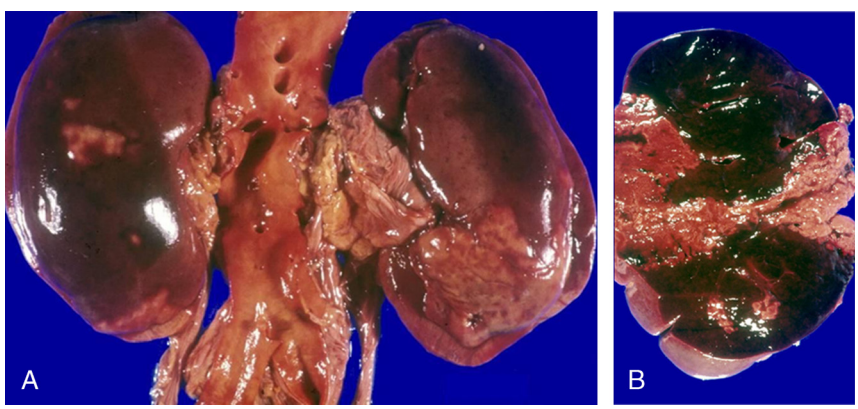

FIGURE 8. Case 3. The patient developed pleuritic pain in the left flank due to a splenic infarct and lumbar pain with hematuria. **A**. Bilateral renal infarcts. Note extensive infarct in the inferior pole of the left kidney. **B**. Splenic infarcts. [This figure can be viewed in color online at http://www.md-journal.com.]

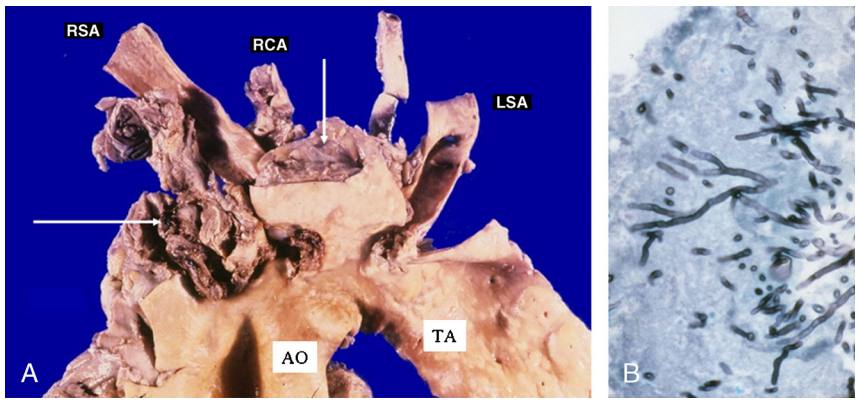

FIGURE 9. Case 5. **A**. Aortitis after bypass grafting. Infection occurred on the suture line of previous aortotomy, and a mycotic aneurysm of the ascending aorta and thoracic arch developed (arrows). The patient presented with fever and peripheral stigmata of endocarditis and died due to aortic rupture. AO = ascending aorta, TA = thoracic aorta, RSA = right subclavian artery, RCA = right carotid artery, LSA = left subclavian artery. **B**. Microscopic view of aortic wall (Grocott stain; original magnification × 100). Typical hyphae dividing at right angles are shown. Cultures yielded *Aspergillus fumigatus*. [This figure can be viewed in color online at http://www.md-journal.com.]

mycotic pseudoaneurysm of the ascending aorta secondary to infective aortitis at the level of the suture-line of previous aortotomy was found. The arterial wall showed a destructive and inflammatory process with abundant hyphae (Figure 9). Cultures of the arterial wall yielded *Aspergillus fumigatus*.

Glomerulonephritis was more common during P1 than during P2. Microscopically, most cases were focal glomerulonephritis, with only 1 case seen in P1 showing signs of diffuse glomerulonephritis due to immune complexes.

Brain Pathology

The brain was examined in 20 cases (Table 5). Ischemic and hemorrhagic infarcts and abscesses were the most common macroscopic findings. Infarcts predominated in the area supplied by the middle cerebral artery and were located in frontal and parietal lobes (Figure 10). Hemorrhagic infarcts were more frequent in patients with PVE on anticoagulant therapy (80%). Subdural hematoma was also found in 1 patient with PVE on dicumarol therapy.

Brain abscesses were observed in 6 (30%) cases and were associated with infections caused by virulent microorganisms such as *S. aureus, P. aeruginosa*, or *Serratia marcescens* (Figure 11).

TABLE 5. Brain Pathology*

Feature	Time Period No. (%)	
	Period 1 (1970–1985) (n = 12)	Period 2 (1986–2008) (n = 8)
Infarcts	7 (59)	5 (62.5)
Bleeding	5 (41.6)	5 (62.5)
PVE	5	3
Abscesses	4 (33)	2 (25)
Subdural hematoma	0	1
Subarachnoid bleeding	1	0
Mycotic aneurysms	1	1
Meningitis	3 (7.5)	2 (25)

*Twelve and 8 brains examined in P1 and P2, respectively.

Neutrophilic meningitis was frequently observed in cases of endocarditis caused by *S. aureus*. Most of these patients also had focal embolic encephalitis located in the convexity of the brain and microabscesses.

The following case report illustrates the presentation of acute endocarditis mimicking acute bacterial meningitis.

Case 6

An 84-year-old man was admitted because of fever, headache, and drowsiness. He had a previous diagnosis of diabetes mellitus, hypertension, and chronic renal failure. Twenty-four hours before admission he suddenly developed spiking fever, chills, and severe headache. On examination he was febrile (39°C) and obtunded. Neck stiffness was noted. No murmurs or peripheral stigmata were observed. Cerebrospinal fluid was mildly cloudy and contained 1500 polymorphonuclear leukocytes, protein 135 mg/dL, and glucose 35 mg/dL. A Gram stain was negative. Treatment with cefotaxime and vancomycin was started. The patient became comatose, renal failure worsened, and he died 48 hours after admission. Blood cultures yielded *S. aureus*. At autopsy, aortic valve endocarditis was found. Multiple cortical cerebral septic emboli with brain abscesses and neutrophilic meningitis were observed.

The diagnosis of IE was not made during life in 14 (35%) cases studied in P1 and in 12 (42.8%) cases in P2. Overall, the diagnosis was missed until autopsy in 38.2% of cases. As mentioned above, IE was hospital acquired in 28 instances. While a clinical diagnosis was made in all but 4 cases of early-onset PVE (23.5%), the diagnosis was not made during life in 22 of 51 patients with native-valve endocarditis (43.1%, p = 0.19). Of these 22 patients with a failed diagnosis, IE was hospital acquired in 11 (50%). The absence of fever, cardiac murmurs, and many of the typical stigmata of endocarditis may have led to the diagnosis being overlooked clinically. Disseminated malignancies, diabetes mellitus, chronic renal failure, hemodialysis, and collagen vascular diseases were the most common comorbidities observed in these cases. Metastatic disease, systemic lupus erythematosus or lupus-like disease, bacterial pneumonia, catheter-associated bacteremia, Gram-negative sepsis, acute brain thrombosis and acute bacterial meningitis were other diagnoses entertained in patients whose diagnosis of endocarditis was not made during life.

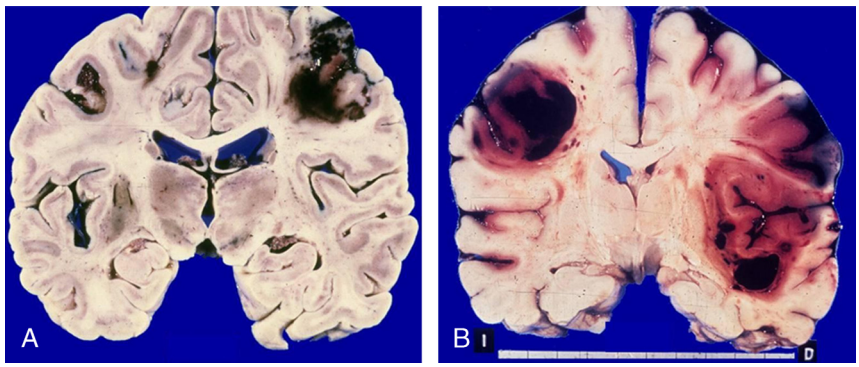

FIGURE 10. A. Frontoparietal infarct in a patient with native-valve enterococcal endocarditis. **B**. Extensive brain hemorrhage in a case of PVE caused by *S. aureus*. Patients on anticoagulant therapy may develop hemorrhagic infarcts. [This figure can be viewed in color online at http://www.md-journal.com.]

Right-sided and mural endocarditis were unexpected findings at autopsy, and a clinical diagnosis was not made in any of these cases. Negative blood cultures contributed to a missed diagnosis of IE in some cases during the early years of this study. Improvement in microbiologic techniques made culture-negative IE a rare condition in P2.

Causes of death are shown in Table 6. Brain emboli and cerebral bleeding, and less frequently myocardial emboli with acute myocardial infarction and acute pulmonary emboli were the most common causes of death in patients with IE. Congestive heart failure was an important determinant of mortality in both periods. The primary cause of death was not definitively established in the postmortem study in a minority of cases (4 in P1 and 1 in P2).

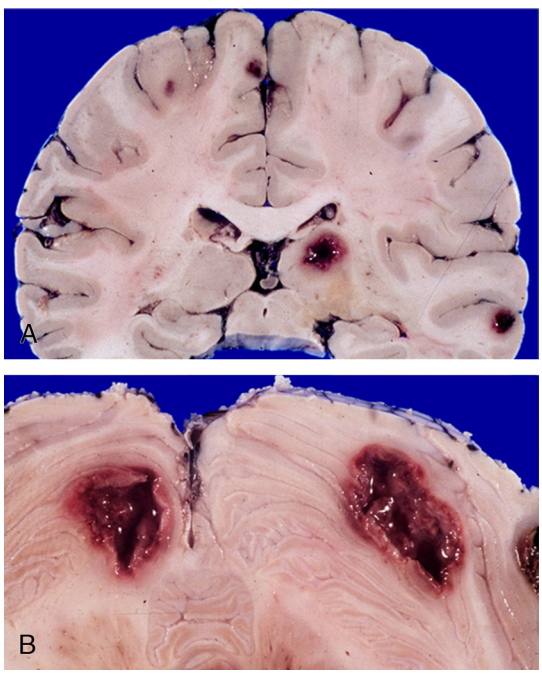

FIGURE 11. A. Multiple brain abscesses—frontal and temporal lobes and thalamus—in a case of PVE caused by *Serratia marcescens*. **B**. Same patient, symmetric abscesses in cerebellum. [This figure can be viewed in color online at http://www.md-journal.com.]

DISCUSSION

Few postmortem studies of IE have been published in recent years, and most have dealt with particular aspects of infection such as predisposing cardiac conditions or specific lesions.[5,76,77] Hence, the frequency with which IE is found at autopsy at the present time is difficult to ascertain. In reports published in the 1960s and 1970s, the frequency ranged from 0.5% to 1.5% in general hospitals[2] but may have been lower in oncology hospitals or higher in specialized cardiovascular hospitals.[59,61] In our institution, IE was observed in 1.3% of autopsied patients.

As shown in this and previous reports, the age of patients with IE has increased in the last 2 decades, and consequently comorbidities are significantly more common now than in the past.[14,43,73,84] Solid neoplasms, chronic renal failure, cirrhosis of the liver, and other chronic debilitating diseases such as diabetes mellitus or collagen vascular diseases are frequently observed in patients with IE.[17,26,38,55,56] These comorbidities increase the mortality of infection and may be an obstacle for accurate clinical diagnosis of IE.[26,56]

Although a preexistent cardiac defect is not always present, IE generally occurs on a predisposing valve disorder.[6,7,45,47] As shown by others, the frequency of rheumatic valve disease has been decreasing while the frequency of degenerative valve disease has been increasing over the years.[43,45–47,73] It is noteworthy that autopsies of PVE decreased from P1 to P2,

TABLE 6. Causes of Death

Cause	Time Period No. (%)	
	Period 1 (1970–1985) (n = 40)	Period 2 (1986–2008) (n = 28)
Emboli	16 (40)	14 (50)
Cardiac failure	10 (25)	6 (21.4)
Pulmonary embolism	3	0
Bleeding	2	1
Septic shock	2	4 (14.2)
Aortic rupture	1	1
Acute renal failure	1	0
Acute myocardial infarction	1	1
Undetermined	4	1

probably due to the lower incidence of early PVE in our institution, which has also been observed in other medical centers in the last decades.[32,42,56] In addition, because prosthetic heart valves are recognized as important predisposing factors for endocarditis, the diagnosis is frequently considered, and patients are appropriately treated; even if they die, autopsy is often not requested.

IE is mainly an infection of the left-side of the heart involving mitral or aortic valve or both simultaneously. Right-sided endocarditis is often an infection associated with intravenous drug use that reached epidemic proportions in recent decades.[16,25,52,58] However, tricuspid valve endocarditis in intravenous drug users is generally a more benign infection with low mortality whose incidence has declined at the turn of the century.[25] Bacteremia associated with central venous catheters, flow-directed pulmonary artery catheterization, pacemakers, and other invasive instrumentation of the heart, are important causes of right-sided endocarditis at the present time.[7,18,23,30,54,62,81,82] We note that, in 6 cases in this series, IE was located on the mural endocardium of the right atrium and eustachian valve with or without simultaneous tricuspid valve and in the left atrial appendage. Eustachian valve endocarditis has been rarely reported in intravenous drug users, but whether the disease is actually rare or whether it is missed because this valve is not routinely studied by echocardiography is not known.[66] All cases in the current series were associated with infected intracardiac venous catheters and *S. aureus* bacteremia, and may be considered the human counterpart of the experimental endocarditis model in animals.[54,75,81,82] Catheters inside the heart produce mechanical damage on the endocardium, which is characterized by hemorrhages and thrombus formation, the so-called nonbacterial thrombotic endocarditis.[45,62] Thrombus composed of platelets and fibrin can be colonized if adherent microorganisms reach the bloodstream and then IE ensues.[45] Due to the absence of cardiac murmurs and the lack of systemic emboli, the diagnosis was commonly missed until autopsy.

The diagnostic usefulness of conventional echocardiography is limited in right-sided mural IE.[52] It has been suggested that multiplane TEE may improve diagnostic accuracy.[51,52,65] We, and others, believe that a systematic examination of the eustachian valve should be included in the echocardiographic survey of patients suspected of having right-sided endocarditis.[66,67] "Breakthrough" or relapsing bacteremia after discontinuation of therapy has been suggested as a major diagnostic hallmark of this particular infection.[23,25,83] Mural endocarditis of the left-side of the heart has been rarely observed, and most cases occurred on ventricular aneurysms and the appendage of the left atrium.[27,78] In the current series, isolated left atrial endocarditis was seen in a patient with chronic atrial fibrillation who developed catheter-associated *S. aureus* bacteremia.[25]

Because most cases occurred on regurgitant valves, vegetations were located on the line of closure of the atrial surface of the mitral valve or on the ventricular surface of the cusps of aortic valve downstream of the regurgitant flow.[13,45,59] In a few cases of mitral insufficiency, McCallum patches were observed. However, infections caused by invasive microorganisms such as *S. aureus* were not limited to valve leaflets, but tended to produce a more severe infection characterized by ulceration, rupture, and perforation of the cusps and necrosis of chordae tendiniae and perivalvular apparatus.[13,57,59] Extension of infection into the surrounding myocardium with abscess formation was seen in native-valve endocarditis and even more frequently in PVE. Large vegetations have been found in IE caused by fungi, *Granulicatella*, and *Abiotrophia* species and HACEK group of microorganisms.[6,9,11] However, we observed the largest vegetations in cases of endocarditis caused by *S. aureus*.[25]

The lesions of PVE had different characteristics.[1,4,42,44,57,68] First, infection occurring on both metallic and biologic prosthetic valves was always located in the sewing ring, and extension into the surrounding myocardium was commonly observed.[1,4,68] Abscess formation and occasional intracardiac fistulae were severe consequences of annular infection.[3,80] Moreover, dehiscense was observed in three-quarters of cases as the result of loosening sutures in infected and friable perivalvular tissue, which dislodged the prosthesis from its anchorage. Cardiac failure was the inevitable consequence of the ensuing valve incompetence.

Remarkably, vegetative lesions of the valve leaflets were not seen in any of the 4 autopsied patients with PVE involving porcine bioprostheses. Isolated involvement of the porcine cusps has been found with variable frequency, and is more common in cases of late-onset PVE. Generally, infections originated from extracardiac foci that reached the cusps through the bloodstream.[12] On the other hand, infection involving both the ring and the leaflets was frequent, and the location seemed to be independent of the timing of acquisition.[29] Our observations suggest that isolated annular involvement in cases of PVE occurring on bioprostheses may result from direct contamination of the sewing ring during the operation or in the immediate postoperative period.[12,44]

Of paramount prognostic importance was the formation of intracardiac fistulae, an unusual but severe complication of PVE of the aortic valve characterized by persistent sepsis, heart block, and refractory cardiac failure.[1,3,4,58,80] In addition, direct extension into the pericardial sac leading to acute purulent pericarditis was mainly found in cases of suppurative aortic endocarditis caused by *S. aureus*.[13]

Obstruction seemed to occur most commonly in cases of PVE of the mitral valve.[1,4] A picture of severe cardiac failure refractory to medical treatment in the absence of new cardiac murmurs was the main manifestation in these cases.

Autopsy revealed the undisputed nature of IE as a multisystem disease. Visceral infarcts and abscesses, along with renal and vascular damage, were commonly seen, and in many instances were unexpected findings not recognized while the patient was alive. The spleen, kidneys, mesentery, and the lung in cases of right-sided endocarditis, were the most common sites for emboli, infarcts, and abscesses. Persistent fever and breakthrough and relapsing bacteremia were the most common and typical manifestations.[25,35,39,40,83] Although rare, acute myocardial infarction was an important cause of mortality or seemed to contribute to death in some patients. Myocarditis and other acute focal lesions have been observed in many cases in whom numerous histologic sections of myocardium were examined.[13] Because this was not routinely performed in our cases, myocarditis was rarely found.

Glomerulonephritis is also an important complication of IE.[50] However, in the current series glomerulonephritis was not a prevalent finding, and, interestingly, we observed a decrease in the number of cases in the second period of study. Focal or segmental proliferation of endothelial and mesangial cells with neutrophilic infiltration and fibrinoid necrosis were the changes most frequently observed. Diffuse, immune complex glomerulonephritis was rarely seen. Observations made in the preantibiotic era suggested that infection with less virulent microorganisms, by virtue of their indolent subacute or chronic course, favored an antibody response predisposing to immune complex glomerulonephritis.[48] Hence, it is possible that

the predominance of cases of acute endocarditis and early treatment with antibiotics may have decreased the number of cases of glomerulonephritis at the present time.[48]

Even more important, due to the greater severity of the lesions, was brain pathology. Symptomatic central nervous system complications have been found in 17%–35% of cases of IE.[36,46,69] Using MRI and neurochemical markers of brain damage, brain emboli have been detected in 65%–80% of cases.[20,69] The incidence of brain emboli is higher in patients with *S. aureus* endocarditis.[20,25] As expected, infarcts predominated in the area supplied by the middle cerebral artery and were located in the frontal and parietal lobes. Some cases developed neutrophilic meningitis resulting from multiple peripheral emboli with microabscess formation extending to the meninges and into subarachnoid space, a pathologic picture resembling focal embolic suppurative encephalitis.

Of catastrophic consequences was brain bleeding, seen mostly in patients with PVE on anticoagulant therapy,[72,74] a major cause of death in the current series. Overall, brain damage due to ischemic infarcts and cerebral hemorrhage was the main cause of death in this series. In comparison, cardiac failure was a less important cause of mortality. Similar observations have been previously reported.[13,59] This is probably due to the increasing use of cardiac surgery to treat cardiac failure resulting from valve insufficiency.[6] Uncontrolled infection, embolization to other vital organs such as myocardium, and the associated chronic debilitating diseases were common causes of death in patients with IE. Missed diagnoses also contributed to mortality in some cases.

Earlier postmortem studies showed that the clinical diagnosis of IE is frequently not made during life. Robinson et al found that diagnosis was not made clinically in 43% of cases, a proportion that was greater in elderly patients.[59,71] But even today, in the era of modern diagnostic technology, IE continues to be a disease whose diagnosis is frequently not made until autopsy. Saad et al[64] reported in 2007 that diagnosis of IE was missed until autopsy in 27% of cases seen in a specialized cardiology hospital. The diagnosis of IE has frequently been missed clinically in patients admitted to intensive care units and in recipients of solid organ transplants.[19,60,63]

In the present study, the clinical diagnosis was missed during life in 38% of cases. Surprisingly, we did not find a decrease in the number of missed diagnoses in the second period of study, when both TTE and TEE were fully available in our institution. In many of these cases, IE was a nosocomial infection presumably acquired during invasive diagnostic or therapeutic procedures such as central venous catheterization, urologic instrumentation, or major surgery.

Health care-associated endocarditis is increasing worldwide and represents one of the major epidemiologic changes of IE in the last 2 decades.[10,14,23,28,30,70] As shown herein, the diagnosis is difficult and the condition may go unrecognized until autopsy.[62] Lack of fever or cardiac murmurs and the absence of typical stigmata of endocarditis often made the diagnosis difficult during life. Moreover, the diagnosis of IE occurring on unusual sites such as the tricuspid valve and in the right atrium is far more difficult to make and often is not suspected during life.[57,58] The diagnostic usefulness of echocardiography is limited in these cases.[52] For these reasons it is tempting to suggest that nosocomial IE represents a medical problem of greater magnitude than previously shown, and that cases may be misdiagnosed.

Importantly, the nonspecific manifestations of IE were frequently attributed to the underlying disease. In these cases, an echocardiogram was often not performed, and if bacteremia was documented, it was considered to be associated with intravenous catheters or focal bacterial infections.

Patients with hospital-acquired enterococcal bacteremia have not been traditionally considered at risk of developing IE, and an echocardiogram was not routinely performed in these individuals.[24] However, there is a significant risk of IE in the elderly with degenerative valve disease in whom the diagnosis of IE may be missed. We believe that an echocardiogram should be performed in this subset of patients with nosocomial enterococcal bacteremia and in other people at risk, such as those with cardiac prostheses.[23] Bacterial pneumonia, Gram-negative sepsis, or acute bacterial meningitis were other diagnoses entertained in cases in which the diagnosis of IE was missed during life. Negative blood cultures contributed to a missed diagnosis of endocarditis in some cases during the early years of this study.

Our observations reinforce the importance of autopsy in providing data for the evaluation of the quality of care, and for teaching and research purposes. Regular comparisons of clinical and autopsy diagnoses may provide pertinent information to improve the future management of patients with IE.

REFERENCES

1. Anderson DJ, Bulkley BH, Hutchins GM. A clinopathologic study of prosthetic valve endocarditis in 22 patients: morphologic basis for diagnosis and therapy. *Am Heart J*. 1977;94: 325–332.
2. Angrist A, Oka M, Nakao K. Prevention and control of bacterial endocarditis. *NY J Med*. 1968;32:922–934.
3. Anguera I, Miro JM, San Roman JA, de Alarcon A, Anguita M, Almirante B, Evangelista A, Cabell CH, Vilacosta I, Ripoll T, Munoz P, Navas E, Gonzalez-Juanatey C, Sarria C, Garcia-Bolao I, Farinas MC, Rufi G, Miralles F, Pare C, Fowler VG Jr, Mestres CA, de Lazzari E, Guma JR, del Rio A, Corey GR. Aorto-Cavitary Fistula in Endocarditis Working Group. Periannular complications in infective endocarditis involving prosthetic aortic valves. *Am J Cardiol*. 2006;98:1261–1268.
4. Arnett EN, Roberts WC. Prosthetic valve endocarditis. Clinicopathologic analysis of 22 necropsy patients with comparison of observations in 74 necropsy patients with active endocarditis involving natural left-sided cardiac valves. *Am J Med*. 1976;38: 281–292.
5. Atkinson JB, Virmani R. Infective endocarditis: changing trends and general approach for examination. *Hum Pathol*. 1987;18: 603–608.
6. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Bolger AF, Levison ME, Ferrieri P, Gerber MA, Tani LY, Gewitz MH, Tong DC, Steckelberg JM, Baltimore RS, Shulman ST, Burns JC, Falace DA, Newburger JW, Pallasch TJ, Takahashi M, Taubert KA; Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease; Council on Cardiovascular Disease in the Young; Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia; American Heart Association; Infectious Diseases Society of America. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. *Circulation*. 2005;111:e394–e434.
7. Baddour LM, Epstein AE, Erickson CC, Knight BP, Levison ME, Lockhart PB, Masoudi FA, Okum EJ, Wilson WR, Beerman LB, Bolger AF, Estes NA III, Gewitz M, Newburger JW, Schron EB, Taubert KA;

American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee; Council on Cardiovascular Disease in Young; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Nursing; Council on Clinical Cardiology; Interdisciplinary Council on Quality of Care; American Heart Association. Update on cardiovascular implantable electronic device infections and their management: a scientific statement from the American Heart Association. *Circulation*. 2010;121:458–477.

8. Battle RM, Pathak D, Humble CG, Key CR, Vanatta PR, Hill RB, Anderson RE. Factors influencing discrepancies between premortem and postmortem diagnoses. *JAMA*. 1987;258:339–344.
9. Bayer AS, Bolger AF, Taubert KA, Wilson W, Steckelberg J, Karchmer AW, Levison M, Chambers HF, Dajani AS, Gewitz MH, Newburger JW, Gerber MA, Shulman ST, Pallasch TJ, Gage TW, Ferrieri P. Diagnosis and management of infective endocarditis and its complications. *Circulation*. 1998;98:2936–2948.
10. Benito N, Miro JM, de Lazzari E, Cabell CH, del Rio A, Altclas J, Commerford P, Delahaye F, Dragulescu S, Giamarellou H, Habib G, Kamarulzaman A, Kumar AS, Nacinovich FM, Suter F, Tribouilloy C, Venugopal K, Moreno A, Fowler VG Jr; ICE-PCS (International Collaboration on Endocarditis Prospective Cohort Study) Investigators. Health care-associated native-valve endocarditis: importance of non-nosocomial acquisition. *Ann Intern Med*. 2009;150:586–594.
11. Boland JM, Chung HH, Robberts FJL, Wilson WR, Steckelberg JM, Baddour LM, Miller DV. Fungal prosthetic valve endocarditis: Mayo Clinic experience with a clinicopathological analysis. *Mycoses*. 2011;54:354–360. [Epub 2010 Apr 6.].
12. Bortolotti U, Thiene G, Milano A, Panizzon G, Valente M, Galluci V. Pathological atudy of infective endocarditis on Hancock porcine bioprostheses. *J Thorac Cardiovasc Surg*. 1981;81:934–942.
13. Buchbinder NA, Roberts WC. Left-sided active infective endocarditis. A study of forty-five necropsy patients. *Am J Med*. 1972;53:20–35.
14. Cabell CH, Jollis JG, Peterson GE, Corey R, Anderson DJ, Sexton DJ, Woods CW, Reller LB, Ryan T, Fowler VG Jr. Changing patient characteristics and the effect on mortality in endocarditis. *Arch Intern Med*. 2002;162:90–94.
15. Cates JE, Christie RV. Subacute bacterial endocarditis. A review of 442 patients treated in 14 centers appointed by the Penicillin Trial Committee of the Medical Research Council. *Quart J Med*. 1951;20:93–130.
16. Cherubin CE, Sapira JD. The medical complications of drug addiction and the medical assessment of the intravenous drug user: 25 years later. *Ann Intern Med*. 1993;119:1017–1028.
17. Chirillo F, Bacchion F, Pedrocco A, Scotton P, De Leo A, Rocco F, Valfre C, Olivari Z. Infective endocarditis in patients with diabetes mellitus. *J Heart Valve Dis*. 2010;19:312–320.
18. Chrissoheris MP, Libertin C, Ali RG, Ghantous A, Bekui A, Donohue T. Endocarditis complicating central venous catheter bloodstream infections: a unique form of health care associated endocarditis. *Clin Cardiol*. 2009;32:e48–54.
19. Combes A, Mokhtari M, Couvelard A, Trouillet JL, Baudot J, Henin D, Gibert C, Chastre J. Clinical and autopsy diagnoses in the intensive care unit: a prospective study. *Arch Intern Med*. 2004;164:389–392.
20. Cooper HA, Thompson EC, Laureno R, Fuisz A, Mark AS, Lin M, Goldstein SA. Subclinical brain embolization in left-sided infective endocarditis: results from the evaluation by MRI of the brains of patients with left-sided intracardiac solid masses (EMBOLISM) pilot study. *Circulation*. 2009;120:585–591.
21. Correl HL, Lubitz JM, Lindert MCF. Bacterial endocarditis: clinicopathologic studies of untreated, treated and cured patients. *Ann Intern Med*. 1951;35:45–58.
22. Fernandez Guerrero ML, Verdejo C, Azofra J, Gorgolas M. Hospital-acquired infectious endocarditis not associated with cardiac surgery: an emerging problem. *Clin Infect Dis*. 1995;20:16–23.
23. Fernandez Guerrero ML, Herrero D, Bellver MT, Gadea I, Fernandez Roblas R, Gorgolas M. Nosocomial enterococcal endocarditis: a serious hazard for hospitalized patients with enterococcal bacteremia. *J Intern Med*. 2002;252:510–515.
24. Fernandez Guerrero ML, Goyenechea A, Verdejo C, Fernandez Roblas R, Gorgolas M. Enterococcal endocarditis on native and prosthetic valves. A review of clinical and prognostic factors with emphasis on hospital-acquired infections as a major determinant of outcome. *Medicine (Baltimore)*. 2007;86:363–377.
25. Fernandez Guerrero ML, Gonzalez Lopez J, Goyenechea A, Fraile J, Gorgolas M. Endocarditis caused by Staphylococcus aureus. A reappraisal of the epidemiologic, clinical, and pathologic manifestations with analysis of factors determining outcome. *Medicine (Baltimore)*. 2009;88:1–22.
26. Fernandez Guerrero ML, Gonzalez Lopez J, Gorgolas M. Infectious endocarditis in patients with cirrosis of the liver: a model of infection in the frail patient. *Eur J Clin Microbiol Infect Dis*. 2010;29:1271–1275.
27. Fernandez Guerrero ML, Aguado JM, Arribas A, Lumbreras C, de Gorgolas M. The spectrum of cardiovascular infections due to Salmonella enterica: a review of clinical features and factors determining outcome. *Medicine (Baltimore)*. 2004;83:123–138.
28. Fernandez Hidalgo N, Almirante B, Tornos P, Pigrau C, Sambola A, Igual A, Pahissa A. Comtemporary epidemiology and prognosis of health care-associated infective endocarditis. *Clin Infect Dis*. 2008;47:1287–1297.
29. Fernicola DJ, Roberts WC. Frequency of ring abscess and cuspal infection in active infective endocarditis involving bioprosthetic valves. *Am J Cardiol*. 1993;72:314–323.
30. Fowler VG Jr, Miro JM, Hoen B, Cabell CH, Abrutyn E, Rubinstein E, Corey GR, Spelman D, Bradely SF, Barsic B, Pappas PA, Anstrom KJ, Wray D, Fortes CQ, Anguera I, Athan E, Jones P, Van der Meer JT, Elliot TS, Levine DP, Bayer AS. Staphylococcus aureus endocarditis. A consequence of medical progress. *JAMA*. 2005;293:3012–3021.
31. Goldman L, Sayson R, Robbins S, Cohn LH, Bettmann M, Weisberg M. The value of the autopsy in three medical eras. *N Engl J Med*. 1983;308:1000–1005.
32. Gordon SM, Serkey JM, Longworth DL, Lytle BW, Cosgrove DM III. Early onset prosthetic valve endocarditis: the Cleveland Clinic experience, 1992–1997. *Ann Thorac Surg*. 2000;69:1388–1392.
33. Grade MH, Zucoloto S, Kajiwara JK, Fernandes MT, Couto LG, Garcia SB. Accuracy of clinical diagnoses of the basic cause of death in a university hospital. *J Clin Pathol*. 2004;57:369–373.
34. Guze LB, Pearce ML. Hospital-acquired bacterial endocarditis. *Arch Intern Med*. 1963;112:56–62.
35. Hawkings C, Huang J, Jin N, Noskin GA, Zembower TR, Bolon M. Persistent Staphylococcus aureus bacteremia: an analysis of risk factors. *Arch Intern Med*. 2007;167:1861–1867.
36. 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;160:2781–2787.
37. Hutchins GM, for the Autopsy Committee of the College of American Pathologists. Practice guidelines for autopsy pathology: autopsy reporting. *Arch Pathol Lab Med*. 1994;118:19–25.
38. Kourany WM, Miro JM, Moreno A, Corey GR, Pappas PA, Abrutyn E, Hoen B, Habib G, Fowler VG Jr, Sexton DJ, Olaison L, Cabell CH; ICE MD Investigators. Influence of diabetes mellitus on the clinical manifestations and prognosis of infective endocarditis: a report from the International Collaboration on Endocarditis-Merged Database. *Scand J Infect Dis*. 2006;38:613–619.
39. Lawrence YR, Pokroy R, Berlowitz D, Aharoni D, Hain D, Breuer GS. Splenic infarction: an update on William Osler's observations. *Isr Med Assoc J*. 2010;12:362–365.

40. Lederman MM, Sprague L, Wallis RS, Ellner JJ. Duration of fever during treatment of infective endocarditis. *Medicine (Baltimore)*. 1992;71:52–57.
41. Lee JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, Bashore T, Corey GR. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30:633–638.
42. Lopez J, Revilla A, Vilacosta I, Villacorta E, Gonzalez-Juanatey C, Gomez I, Rollan MJ, San Roman JA. Definition, clinical profile, microbiological spectrum, and prognostic factors of early-onset prosthetic valve endocarditis. *Eur Heart J*. 2007;28:760–765.
43. Lopez J, Revilla A, Vilacosta I, Sevilla T, Villacorta E, Sarria C, Pozo E, Rollan MJ, Gomez I, Mota P, San Roman JA. Age-dependent profile of left-sided infective endocarditis: a 3-center experience. *Circulation*. 2010;121:892–897.
44. Lytle BW, Priest BP, Taylor PC, Loop FD, Sapp SK, Stewart RW, McCarthy PM, Muehrcke D, Cosgrove DM III. Surgical treatment of prosthetic valve endocarditis. *J Thorac Cardiovasc Surg*. 1996;111:198–207.
45. Moreillon P. Infective endocarditis. *Lancet*. 2004;363:139–149.
46. Murdoch DR, Corey GR, Hoen B, Miro JM, Fowler VG Jr, Bayer AS, Karchmer AW, Olaison L, Pappas PA, Moreillon P, Chambers ST, Chu VH, Falco V, Holland DJ, Jones P, Klein JL, Raymond NJ, Read KM, Tripodi MF, Utili R, Wang A, Woods CW, Cabell CH; International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) Investigators. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. *Arch Intern Med*. 2009;169:463–473.
47. Mylonakis E, Calderwood SB. Infectious endocarditis in adults. *N Engl J Med*. 2001;345:1318–1330.
48. Nasr SH, Markowitz GS, Stokes MB, Said SM, Valeri AM, D'Agati VD. Acute postinfectious glomerulonephritis in the modern era: experience with 86 adults and review of the literature. *Medicine (Baltimore)*. 2008;87:21–32.
49. Netzer RO, Zollinger E, Seiler C, Cerny A. Infective endocarditis: clinical spectrum, presentation and outcome. *Heart*. 2000;84:25–30.
50. Neugarten J, Baldwin DS. Glomerulonephritis in bacterial endocarditis. *Am J Med*. 1984;77:297–304.
51. Palakodeti V, Keen WD, Rickman LS, Blanchard DG. Eustachian valve endocarditis: detection with multiplane transesophageal echocardiography. *Clin Cardiol*. 1997;20:579–580.
52. Panidis IP, Kotler MN, Mintz GS, Segal BL, Ross JJ. Right heart endocarditis: clinical and echocardiographic features. *Am Heart J*. 1984;107:759–764.
53. Pankey GA. Subacute bacterial endocarditis at the University of Minnesota Hospital, 1939 through 1959. *Am Heart J*. 1962;64:583–591.
54. Power J, Wing EJ, Talamo TS, Stanko R. Fatal bacterial endocarditis as complication of permanent indwelling catheters: report of two cases. *Am J Med*. 1986;81:166–168.
55. Rekik S, Trabelsi I, Hentati M, Hammami A, Jemaa MB, Hachicha J, Kammoun S. Infective endocarditis in hemodialysis patients: clinical features, echocardiographic data and outcome: a 10-year descriptive analysis. *Clin Exp Nephrol*. 2009;13:350–354.
56. Rivas P, Alonso J, Moya J, Gorgolas M, Martinell J, Fernandez Guerrero ML. The impact of hospital-acquired infections on the microbiology and prognosis of late-onset prosthetic valve endocarditis. *Chest*. 2005;128:764–771.
57. Roberts WC. Characteristics and consequences of infective endocarditis (active, healed or both) learned from morphologic studies. In: Rahimtoola SA, ed. *Infective Endocarditis*. New York: Grune & Stratton; 1978:55–123.
58. Roberts WC, Buchbinder NA. Right-sided valvular infective endocarditis. A clinicopathologic study of twelve necropsy patients. *Am J Med*. 1972;53:7–19.
59. Robinson MJ, Greenberg JJ, Korn M, Rywyl AM. Infective endocarditis at autopsy: 1965-1969. *Am J Med*. 1972;52:492–498.
60. Rosen J, Frans E, Wilner A, Knockaert DC, Bobbaers H. Comparison of premortem clinical diagnoses in critically ill patients and subsequent autopsy findings. *Mayo Clin Proc*. 2000;75:562–567.
61. Rosen P, Armstrong MD. Infective endocarditis in patients treated for malignant neoplastic diseases: a postmortem study. *Am J Clin Pathol*. 1973;60:241–250.
62. Rowley KM, Clubb KS, Walker Smith GJ, Cabin HS. Right-sided infective endocarditis as a consequence of flow-directed pulmonary artery catheterization: a clinicopathological study of 55 autopsied patients. *N Engl J Med*. 1984;311:1152–1156.
63. Ruttmann E, Bonatti H, Legit C, Ulmer H, Stelzmueller I, Antretter H, Margreiter R, Laufer G, Mueller LC. Severe endocarditis in transplant recipients—an epidemiologic study. *Transpl Int*. 2005;18:690–696.
64. Saad R, Yamada AT, Ferraz Pereira da Sousa FH, Sampaio Gutierrez P, Mansur AJ. Comparison between clinical and autopsy diagnoses in a cardiology hospital. *Heart*. 2007;93:1414–1419.
65. Sampedro MF, Patel R. Infections associated with long-term prosthetic devices. *Infect Dis Clin North Am*. 2007;21:785–819.
66. San Roman JA, Vilacosta I, Sarria C, Garcimartin I, Rollan MJ, Fernandez-Aviles F. Eustachian valve endocarditis: is it worth searching for? *Am Heart J*. 2001;142:1037–1040.
67. San Roman JA, Vilacosta I, Zamorano JL, Almeria C, Sanchez-Harguindey L. Transesophageal echocardiography in right-sided endocarditis. *J Am Coll Cardiol*. 1993;21:1226–1230.
68. San Roman JA, Vilacosta I, Sarria C, de la Fuente L, Sanz O, Vega JL, Ronderos R, Gonzalez Pinto A, Jesus Rollan M, Graupner C, Batlle E, Lahulla F, Stoermann W, Portis M, Fernandez-Aviles F. Clinical course, microbiologic profile, and diagnosis of periannular complications in prosthetic valve endocarditis. *Am J Cardiol*. 1999;83:1075–1079.
69. Snygg-Martin U, Gustafsson L, Rosengren L, Alsio A, Ackerholm P, Andersson R, Olaison L. Cerebrovascular complications in patients with left-sided infective endocarditis are common: a prospective study using magnetic resonance imaging and neurochemical brain damage markers. *Clin Infect Dis*. 2008;47:23–30.
70. Sy RW, Kritharides L. Health care exposure and age in infective endocarditis: results of a contemporary population-based profile of 1536 patients in Australia. *Eur Heart J*. 2010;31:1890–1897.
71. Thell R, Martin FH, Edwards JE. Bacterial endocarditis in subjects 60 years of age or older. *Circulation*. 1975;51:174–182.
72. Thuny F, Avierinos JF, Tribouilloy C, Giorgi R, Casalta JP, Milandre L, Brahim A, Nadji G, Riberi A, Collart F, Renard S, Raoult D, Habib G. Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: a prospective multicentre study. *Eur Heart J*. 2007;28:1155–1161.
73. Tleyjeh I, Steckelberg JM, Murad HS, Anavekar NS, Ghomrawi HMK, Mirzoyev Z, Moustafa SE, Hoskin TL, Mandrekar JN, Wilson WR, Baddour LM. Temporal trends in infective endocarditis. A population-based study in Olmsted County, Minnesota. *JAMA*. 2005; 293:3022–3028.
74. Tornos P, Almirante B, Mirabet S, Permanyer G, Pahissa A, Soler J. Infective endocarditis due to Staphylococcus aureus. Deleterious effect of anticoagulant therapy. *Arch Intern Med*. 1999;159:473–475.
75. Tsao MMP, Katz D. Central venous catheter-induced endocarditis: human correlate of the animal experimental model of endocarditis. *Rev Infect Dis*. 1984;6:783–790.
76. Vaideeswar P, Mishra P, Nimbalkar M. Infective endocarditis of the Dacron patch. A report of 13 cases at autopsy. *Cardiovasc Pathol*. 2011;20:e169–e175. [Epub 2010 Sep 1].

77. Vaideeswar P, Jawale RM, Tullu M. Isolated infective endocarditis of the pulmonary valve: an autopsy analysis of nine cases. *Cardiovasc Pathol*. 2009;18:231–235.
78. Venezio FR, Thompson JE, Sullivan H, Subramanian R, Ritzman P, Gunnar RM. Infection of a ventricular aneurysm and cardiac mural thrombus. *Am J Med*. 1984;77:551–554.
79. Von Reyn CF, Levy BS, Arbeit RD, Friedland G, Crumpacker CJ. Infective endocarditis: an analysis based on strict case definitions. *Ann Intern Med*. 1981;94:505–518.
80. Wang A, Athan E, Pappas PA, Fowler VG Jr, Olaison L, Pare C, Almirante B, Munoz P, Rizzi M, Naber C, Logar M, Tattevin P, Iarussi DL, Selton-Suty C, Jones SB, Casabe J, Morris A, Corey GR, Cabell CH; International Collaboration on Endocarditis-Prospective Cohort Study Investigators. Contemporary clinical profile and outcome of prosthetic valve endocarditis. *JAMA*. 2007;297:1354–1361.
81. Watanakunakorn C, Baird IM. Staphylococcus aureus bacteremia and endocarditis associated with a removable infected intravenous device. *Am J Med*. 1977;63:253–256.
82. Watanakunakorn C. Infective endocarditis as a result of medical progress. *Am J Med*. 1978;64:917–919.
83. Watanakunakorn C, Tan JS, Phair JP. Some salient features of Staphylococcus aureus endocarditis. *Am J Med*. 1973;54:473–481.
84. Werner GS, Schultz R, Fuchs JB, Andreas S, Prange H, Ruschewski W, Kreuzer H. Infective endocarditis in the elderly in the era of transesophageal echocardiography: clinical features and prognosis compared with younger patients. *Am J Med*. 1996;100:90–97.
85. Weustink AC, Hunik MG, van Dijke CF, Renken NS, Krestin GP, Oosterhuis JW. Minimally invasive autopsy: an alternative to conventional autopsy? *Radiology*. 2009;137:1275–1276.

