

Research

Complicated infective endocarditis necessitating ICU admission: clinical course and prognosis

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Abstract

Aim: To study incidence, clinical course and prognostic factors in patients admitted to medical intensive care units (ICUs) because of a complicated course of infective endocarditis.

Method: This was a retrospective multicenter observational study of 4106 patients admitted to four medical ICUs in one tertiary hospital and one university hospital between 1994 and 1999.

Results: Infective endocarditis was identified in 33 (0.8%) patients. Of these, 26 were male, mean age was 59 ± 12 and APACHE-III score was 75 ± 31 . Reasons for transfer to the ICU were congestive heart failure in 64%, septic shock in 21%, neurological deterioration in 15% and cardiopulmonary resuscitation in 9%. Inotropes or vasoconstrictors were required in 73% and multiorgan failure developed in 64% of the patients. Prosthetic valve endocarditis was present in 21%. Gram-positive cocci were found in 96% of all positive cultures; cultures were negative in 27% of the patients. Transthoracic echocardiograms were diagnostic in only 33% and transesophageal studies were required in 91% to confirm diagnosis or fully to delineate the extent of disease. Surgical intervention was performed in 60% of the patients, and the remaining 40% were only treated medically. The APACHE-III score on admission did not differ statistically between the two groups (69 ± 30 versus 84 ± 34 , $P = 0.17$). In-patient mortality was 84% in patients treated medically, and 35% in surgically treated patients. Using multivariate analysis, acute renal failure on admission was identified as the independent single predictor for in-patient death (OR 5, 95% CI 1.04–24.03, $P = 0.04$).

Conclusion: The prognosis for patients with infective endocarditis requiring admission to a medical ICU is serious. Nevertheless, the data suggest that surgical intervention may be successfully performed in a substantial number of patients despite the presence of severe shock and occurrence of multiorgan failure.

Keywords infection, endocarditis, critically ill, outcome assessment

Introduction

Infective endocarditis (IE) represents the fourth leading cause of life-threatening infectious disease in the US [1]. Despite advances in diagnosis and treatment, IE still carries a high

morbidity and mortality rate [2]. Factors that are strongly associated with poor outcome are the presence of uncontrolled infection or development of congestive heart failure that may require transfer to the ICU. When complications

have developed, results of medical therapy are unsatisfactory, with mortality in up to 90% of cases [3,4]. Although several studies have suggested that a more aggressive surgical approach may improve prognosis, the tendency to postpone surgery in the hope of improving the hemodynamic status and of controlling the septic condition persists [5]. Systematic data on this subject are not available, so assessments were made of incidence, clinical course and outcome of patients admitted to medical intensive care units (ICUs) because of a complicated course of IE.

Materials and methods

Subjects

We reviewed ICU records of all patients with the diagnosis of IE who were admitted to four medical ICUs in Vienna between January 1994 and January 1999. Patients were selected for the study if they fulfilled the Duke criteria for definite endocarditis published in detail elsewhere [6]. Pathological criteria included either demonstrable microorganisms or pathological lesions compatible with active endocarditis. For clinical diagnosis of endocarditis, two major criteria, one major and three minor criteria or five minor criteria were required. Major criteria included positive blood cultures (typical microorganisms or persistently positive blood cultures) and evidence of endocardial involvement (positive echocardiogram for IE or new valvular regurgitation). Minor criteria included presence of predisposing cardiac disease, intravenous drug use, fever, vascular phenomena, immunological phenomena, microbiological evidence, and echocardiographic criteria not fulfilling the major criteria. The routine microbiologic screening also included fastidious organisms, anaerobes, fungi, and organisms from the HACEK group, whereas screening for bartonella, legionella and brucella was not routinely performed.

Patients who were preoperatively admitted to the ICU because of scheduled cardiac surgery as well as patients transferred to the ICU after cardiac surgery were excluded. After having applied the above-mentioned criteria to all available patient charts, 33 patients with the definite diagnosis of IE were identified.

Clinical data

Clinical data were obtained from a review of the patients' medical records. This review included demographic data, presence of inclusion and exclusion criteria, APACHE-III score and Glasgow coma score on ICU admission, duration of illness and duration of ICU-stay, multiple laboratory data, echocardiographic findings, microbiological findings, timing and type of surgery. Heart failure was defined by the presence of hypotension (systolic arterial pressure <90 mmHg and/or need for inotropic or vasopressor therapy) and pulmonary congestion consistent with edema on a chest X-ray. Septic shock was defined as hypotension (systolic arterial pressure <90 mmHg and/or need for vasopressor therapy), fever (>38.3°C) or hypothermia (<35.5°C), tachycardia

(>90 beats/min) and tachypnoea (>20/min). Renal failure was defined as oliguria (<20 ml/h) accompanied by an increase in serum creatinine of at least 44 µmol/L above baseline and/or severe renal dysfunction requiring extracorporeal renal support. Respiratory failure was defined as a PaO₂/F_iO₂ less than 200 while breathing spontaneously and/or the need for mechanical ventilation. Multiorgan failure was defined as more than three points of Goris score [7]. Major embolic events were defined by both clinical symptoms (sudden neurologic deficit, ischemia in the peripheral circulation) and definitive findings on diagnostic imaging procedures (computed tomography of the brain; coronary angiogram; sonography or computed tomography of the abdomen, sonography of peripheral arteries).

Echocardiography

Transthoracic echocardiography and transesophageal echocardiography were performed using one of three available systems (VINGMED 800, DIASONICS, Horten, Norway; ACUSON 2500, Mountain View, CA; SONOS 5500, Hewlett Packard, Andover, MA). Transthoracic echocardiography was performed immediately before transesophageal echocardiography in 31/33 patients. Besides all standard views, multiple additional views were required in many patients to delineate the full extent of cardiac involvement. Valvular vegetations were defined as soft mobile masses attached to the endocardium distinct in echogenicity from the cardiac valves with motion independent of cardiac structures. Valvular regurgitation was assessed using standard criteria [8]. Abscess formation was diagnosed by presence of an echo-free space in the paravalvular region or abnormal paravalvular echogenicity measuring more than 10 mm [9].

Statistical analysis

Data are shown as percentage or mean ± standard deviation. The chi-square test and Fisher's exact test were used in cases of categorical variables. Univariate analysis was used to determine risk factors for ICU-mortality. Variables suggested by the univariate analysis ($P < 0.10$) were entered into a forward stepwise multiple logistic regression analysis model. A P -value <0.05 was considered significant.

Results

Clinical characteristics

Among 4106 patients hospitalized in four medical ICUs during the 4-year study period, 33 (0.8%) patients, 26 men and seven women were admitted because of a complicated course of IE. Two of these patients had a previous episode of IE. In 18 (55%) patients, presence of IE was already established on admission, whereas 15 (45%) cases were newly diagnosed after transfer to the ICU. Demographic characteristics, clinical features and laboratory data within 24 h after ICU admission are presented in Table 1. Reasons for transfer to the ICU of the 33 patients were: congestive heart failure in 21 (64%) cases; septic shock in seven (21%) cases; neurological deterioration in five (15%) cases and in-patient car-

Table 1

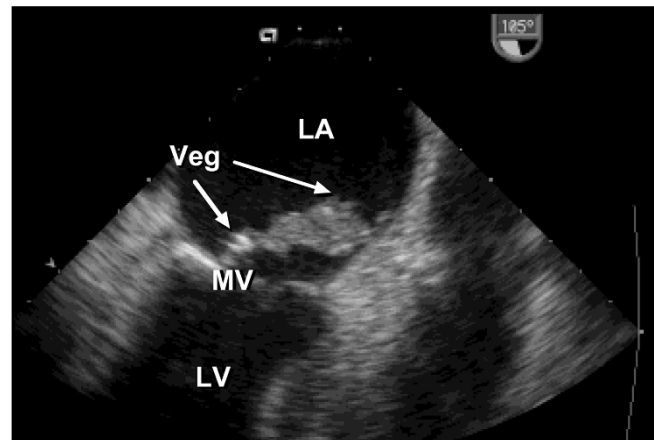
Characteristics of patients on admission	
Male/female	26/7
Age (years)	59.1 ± 12.7 (28–79)
APACHE III score (points)	75 ± 31 (31–150)
Temperature (°C)	37.2 ± 1.3 (34.4–39.7)
Platelets (×10 ⁹ /l)	148 ± 101 (32–395)
WBC (×10 ⁹ /l)	16.8 ± 9.3 (3.3–48.0)
Heart rate (bpm)	106 ± 24 (30–150)
C-reactive protein (mg/dl)	11.1 ± 7.4 (0.5–29.2)
Glasgow coma score	12 ± 3 (3–15)
Illness duration (days)	22 ± 26 (0–109)
AV-block II or III	6 (18)
Acute renal failure	13 (39)
Multiorgan failure	21 (64)

Continuous variables are presented as mean ± SD (range) and categorical measures are presented as *n* (%). AV, atrioventricular; WBC, white blood cell count.

diopulmonary resuscitation in three (9%) cases. Thirteen (39%) patients had acute renal failure, 26 (79%) patients were mechanically ventilated, and 24 (73%) patients required administration of positive inotropes or vasoconstrictors [epinephrine *n* = 16 (1.02 ± 1.4 µg/kg per min); norepinephrine *n* = 18 (0.93 ± 1.184 µg/kg per min); dobutamine *n* = 13 (6.0 ± 3.1 µg/kg per min); dopamine *n* = 20 (7.5 ± 5.0 µg/kg per min)]. Twenty-six (79%) patients had native valve endocarditis (NVE) and seven (21%) had prosthetic valve endocarditis (PVE). In NVE the aortic valve was infected in 14 patients and the mitral valve in nine patients and both the aortic and the mitral valve were infected in three patients. In PVE the aortic valve was involved in six patients and the mitral valve in one patient. Six patients with PVE had a bioprosthesis and one patient had a mechanical prosthesis.

Microbiological results

Staphylococcus aureus (one methicillin-resistant strain) was identified as the most common infecting organism in 12 (36%) patients (nine patients with NVE and three patients with PVE). *Viridans streptococci* were encountered in five (15%) patients (all with NVE), *enterococci* in four (12%) patients (three patients with NVE and one patient with PVE). *Corynebacterium* and *Staphylococcus warneri* were each found in one patient. Culture-negative IE was observed in 10 (27%) patients (seven patients with NVE and three patients with PVE). Cultures of tissue obtained at surgery (*n* = 4) or at autopsy (*n* = 6) were negative in all cases. Six of the patients with negative cultures had received prior antibiotic therapy for 14.7 ± 15 days. Duration of disease before ICU admission tended to be shorter in patients with culture-negative IE (median illness duration 5 versus 13 days, *P* = 0.12).

Figure 1

Transesophageal long axis view in a patient with severe heart failure and mitral incompetence showing a large vegetation (at arrows) attached to the posterior mitral valve leaflet. LA, left atrium; LV, left ventricle; MV, mitral valve; Veg, vegetation.

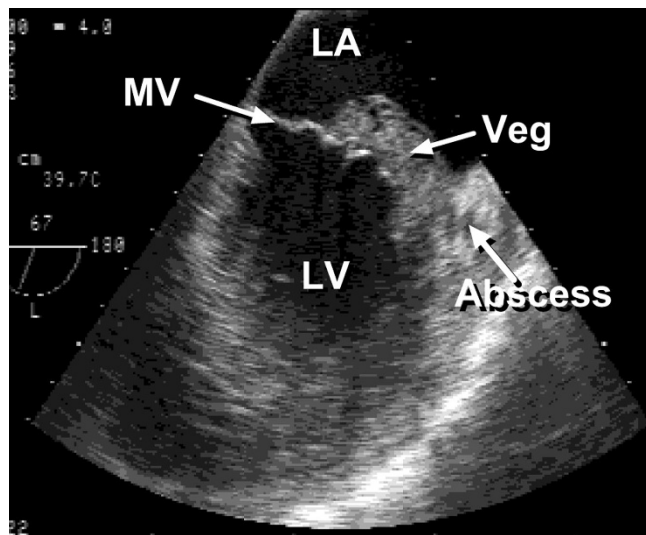
Echocardiography

The echocardiogram was indicative for IE in all patients. Typical findings are presented in Figures 1 and 2. Diagnosis of IE was established by transthoracic study in 11 (33%) patients and by transesophageal echocardiography in 22 (67%) patients. However in eight patients with an already diagnostic transthoracic echocardiography, additional transesophageal echocardiography was required for complete assessment of extent of disease. Valvular vegetations were seen in 25 (76%) patients, of whom 13 had aortic valve involvement, 10 had mitral valve involvement and two had combined aortic and mitral valve involvement. Transesophageal findings missed by the initial transthoracic echocardiography were valvular vegetations in 17 cases, flail leaflets in two cases, and abscess formation in 10 cases. Maximum diameter of the vegetation was >10 mm in 12 patients and <10 mm in 13 patients. There was a trend towards a higher risk of subsequent systemic embolism in patients with a vegetation size >10 mm (OR 5.5, 95% CI 0.96–31.43, *P* = 0.07). Cavities indicating abscess formation were found in 18 patients (54%). Severe valvular regurgitation (grade 3 or 4) of the aortic valve (*n* = 13) and/or mitral valve (*n* = 8) was present in 20 (60%) patients.

Clinical course

All patients received antibiotics according to microbiological findings or when culture negative according to standard antibiotic regimens using either penicillin G, flucloxacillin or vancomycin/teicoplanin in combination with aminoglycosides. Overall 20 (60%) patients, 14 with NVE and six patients with PVE, underwent valvular surgery 6 ± 9 (range: 0–38) days after admission to the ICU. Main indications for surgery were congestive heart failure in 13 cases, uncontrolled sepsis in

Figure 2



Transesophageal long axis view in a patient with sepsis demonstrating a large vegetation attached to the anterior mitral valve leaflet and an echo-free space in the mitral valve annulus infiltrating the surrounding myocardium consistent with the presence of an abscess. Abscess formation was confirmed at surgery. LA, left atrium; LV, left ventricle; MV, mitral valve; Veg, vegetation.

four cases and recurrent embolism in three cases. Main reasons for deferring surgery were a questionable neurological outcome in three patients and a severe comorbid status in two patients. Two patients were clinically stable and were judged not to require emergency surgery. Six other patients died before surgery could be performed. Clinical and laboratory characteristics of patients undergoing surgical or non-surgical treatment are compared in Table 2. No significant differences and only a trend towards a higher APACHE III score in non-surgical patients were observed. Surgical treatment comprised isolated aortic valve replacement in nine patients, isolated mitral valve replacement in six patients and a combined valvular procedure in five patients. For aortic valve replacement a bioprosthesis was used in seven patients, a homograft in six patients and mechanical prosthesis in one patient. Mitral valve surgery included mitral valvular repair in six patients and mitral valve replacement with a mechanical prosthesis or a bioprosthesis in three and two patients, respectively.

Prognostic factors

Eighteen (54%) patients died during the hospital stay, 7/20 (35%) after valvular surgery and 11/13 (84%) in the medically treated group. By univariate analysis significant associations between in-patient mortality and a white blood cell count (WBC) of $>15 \times 10^9/l$ and the presence of acute renal failure were observed. Multivariate analysis identified acute renal failure on admission as the single independent risk factor for death (Table 3). Seven patients died as a result of cardiogenic shock and seven from septic shock. One patient

Table 2

Characteristics of patients with and without surgical treatment

Parameter	Without surgery (n = 13)	With surgery (n = 20)	P-value
Age (yr)	60.4 ± 13.3	58.4 ± 12.6	0.55
APACHE III score (points)	84 ± 34	69 ± 30	0.17
Temperature (°C)	37.1 ± 1.2	37.2 ± 1.5	0.78
Platelets ($\times 10^9/l$)	162 ± 116	139 ± 92	0.67
WBC ($\times 10^9/l$)	18.7 ± 12.8	15.6 ± 6.2	0.27
Heart rate (bpm)	106 ± 34	106 ± 17	0.74
C-reactive protein (mg/dl)	13.7 ± 7.4	9.4 ± 7.1	0.06
Illness duration (days)	18.1 ± 24.2	24.5 ± 28.4	0.45
AV-block II or III	2	4	0.81
Acute renal failure	6	7	0.47
Catecholamine therapy	9	15	1.00
Mechanical ventilation	12	14	0.15
Congestive heart failure	8	13	0.56
Septic shock	1	6	0.14
Multiorgan failure	11	10	0.07
CPR before admission	3	0	0.06
Aortic valve endocarditis	9	14	0.96
Mitral valve endocarditis	6	8	0.73
Native valve endocarditis	11	14	0.30
Prosthetic valve endocarditis	2	5	0.42

Continuous variables are presented as median ± SD (range), and categorical measures are presented as n. AV, atrioventricular; CPR, cardiopulmonary resuscitation; WBC, white blood cell count.

in the surgical group and one in the non-surgical group died as a result of uncontrolled bleeding. Among the surviving patients, two (one conservatively treated and one surgically treated patient) had a Glasgow Coma Score of <14 at transfer out of the ICU.

Discussion

The study presented here examined the clinical course and prognosis for patients requiring admission to an ICU because of IE. To our knowledge it represents the first systematic analysis of this small but important subset of ICU patients and highlights the serious prognosis of patients with a complicated course of IE.

Cardiogenic and septic shock were the main reasons for intensive care treatment. Male preponderance and age distribution in this study were comparable to non-ICU series [2]. All patients in this study had left-sided valvular endocarditis and the aortic valve was most commonly involved. PVE was frequent, which might be explained by the location of three of

Table 3**Risk factors for in-patient death**

Parameter	Survived (<i>n</i> = 15)	Died (<i>n</i> = 18)	UV (<i>P</i> -value)	MV (<i>P</i> -value)	OR (95%CI)
Age (yr)	56 ± 13	62 ± 12	0.36		
Temperature (°C)	37.5 ± 1.2	36.9 ± 1.5	0.36		
Platelets (×10 ⁹ /l)	153 ± 99	144 ± 106	0.80		
Heart rate (bpm)	109 ± 16	104 ± 30	0.60		
C-reactive protein (mg/dl)	11.7 ± 8.9	10.6 ± 6.2	0.37		
Illness duration (days)	28 ± 31	18 ± 22	0.45		
AV-block	1	5	0.18		
Acute renal failure	3	10	0.03	0.04	5 (1.04–24.03)
Congestive heart failure	10	11	0.74		
Septic shock	4	3	0.67		
Systemic emboli	10	10	0.51		
CPR before admission	0	3	0.23		
Aortic valve endocarditis	9	14	0.44		
Mitral valve endocarditis	7	7	0.65		
Native valve endocarditis	11	14	1.00		
Prosthetic valve endocarditis	3	4	1.00		
Cavities on echo	6	10	0.37		
Vegetation on echo	13	13	0.41		
WBC >15×10 ⁹ /l	4	11	0.04	0.18	2.9 (0.60–54.0)
<i>Staphylococcus aureus</i>	7	5	0.26		
<i>Streptococcus viridans</i>	2	3	0.68		
Culture-negative endocarditis	5	5	1.0		
Early appropriate antibiotics	10	8	0.2		

Continuous variables are presented as median ± SD (range), and categorical measures are presented as *n*. AV, atrioventricular; CI, confidence interval; CPR, cardiopulmonary resuscitation; MV, multivariate analysis; OR, odds ratio; UV, univariate analysis; WBC, white blood cell count.

the participating ICUs in a university hospital environment. Surprisingly, no cases of right-sided IE were observed, which is reported to be frequent in intravenous drug abusers [10]. The two patients with a history of intravenous drug abuse included in the series had left cardiac involvement.

In all the patients in the study with positive blood culture Gram-positive strains were present and *Staphylococcus aureus* was identified as the most prevalent pathogen. The proportion of culture-negative endocarditis in this cohort was slightly higher than in previous reports [2], which may be explained by the high incidence of antimicrobial pretreatment and by the fact that these patients tended to have a shorter illness duration making a detailed microbiologic evaluation more difficult. In a previous study, 62% of patients with culture-negative endocarditis had received prior antibiotic therapy compared to only 31% of patients with culture-positive endocarditis [11].

Previous studies also reported a worse prognosis in patients with IE secondary to infection with certain microorganisms such as *Staphylococcus aureus* [9]. The study reported here failed to show an association between bacteriological findings and outcome. It is likely that any differences in mortality will diminish in the presence of a complicated clinical course of the disease.

The study also highlights the usefulness of the transesophageal echocardiography approach for diagnosis and risk stratification of IE. Transesophageal echocardiography was required in more than 90% of the patients, either to ascertain the pending diagnosis or to delineate the full extent of disease. Vegetations were seen by transthoracic or transesophageal echocardiography in 79% of the patients. In line with previous series, systemic embolism appeared to increase by more than fivefold in patients with vegetations >10 mm in size. Abscess formation was also a frequent

finding on transesophageal echocardiography in this cohort of ICU patients.

The observed overall in-patient mortality of 54% in this series is high, but cannot be compared with data obtained in other series because the analysis here included only the patients with severest IE, who required admission to an ICU. Multivariate analysis showed that presence of acute renal failure on admission was the single independent greatest risk factor for a fatal outcome. More than half of the patients in the study underwent successful surgical treatment. In other series, which included patients with IE associated with severe heart failure, in-patient mortality after surgery reached 41% [12,13].

Patients admitted to an ICU as a result of a complicated course of IE, may frequently require acute cardiac surgery for correction of massive valvular regurgitation or for prevention of recurrent systemic embolism. Abscess drainage and/or removal of prosthetic endovascular material may be necessary for treatment of uncontrolled sepsis. Antibiotic pretreatment lasting for several days before cardiac surgery is recommended by some authors [12], but several of the patients in this study had to be operated on immediately after initiation of antibiotic therapy. Nevertheless, cardiac surgery is often deferred in the setting of severe shock and/or of multi-organ failure and patient transfer to a cardiac surgery facility may be associated with additional risks. The decision whether to perform acute surgery is particularly difficult in unconscious or sedated patients with an uncertain neurologic outcome. In the study series cardiac surgery was most often deferred in these patients.

In conclusion, our results show that despite improvements in diagnostic and surgical techniques, advances in antibiotic therapy and optimized critical care, IE still involves a poor prognosis once major complications such as heart failure, septic shock or recurrent systemic embolism have developed. Diagnostic work-up, including a complete transthoracic and transesophageal study, must be performed immediately in every patient admitted to an ICU with embolism, heart failure, cardiogenic or septic shock of unknown cause, as the data presented here suggest that prompt surgical intervention can be life-saving in patients with IE despite the presence of severe shock and the occurrence of multiorgan failure.

Competing interests

None declared.

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