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Clinical Features of Patients with Infective Endocarditis in Emergency Department

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Abstract

Objective: Infective endocarditis (IE) is a rare but life-threatening multisystem disease that results from infection of the endocardial surface of the heart. IE manifests with varied and uncommon symptoms so it is a tricky situation for emergency physicians; our goal is to present the clinical features and course of IE patients in emergency department.

Methods: This study was conducted retrospective and descriptive study was between January 1, 2010 and December 31, 2019. Patients aged over 18 years and diagnosed with definite IE or possible IE according to the modified Duke criteria were enrolled in the study. We statistically analyse the difference between non-survivors and survivors groups for age, gender, symptoms, co-existing conditions, laboratory and imaging results and IE related complications and surgical intervention.

Results: Twenty-nine patients enrolled in the study 20 patients (69%) were admitted with definite IE, and 9 patients (31%) met just possible IE diagnosis according to modified Duke's criteria. Five (17%) patients died from IE and related complications. *Staphylococcus aureus* subspecies are the prominent agents in the blood culture results. Twenty five of patients (86%) had significant echocardiographic findings. Mitral and aortic valves the most affected parts of the endocardial surface in our study.

Conclusion: IE should be considered in patients with fever and predisposing heart conditions. IE related complications may change the course of the disease. Surgical intervention reduces the mortality rate so that it is beneficial for selected patients.

Keywords: Infective endocarditis, emergency department, *Staphylococcus aureus*, mortality

INTRODUCTION

Infective endocarditis (IE) is an uncommon multisystem problem that results from infection of the endocardial surface of the heart (1). The term of "endocarditis" was originally used in the early 19th century. It is referred to the inflammatory processes in the endocardial tissue of the symptomatic patients after clinical anatomy based autopsy studies (2). Considering medical advances, IE has evolved and changed its patient profiles and clinical characteristics over the decades. At the present times prosthetic valve replacement, indwelling devices, hemodialysis, venous catheters, immunosuppression, and intravenous (IV) drug use have become the principal risk factors (3-5). IE is an uncommon disease that diagnosing is quite difficult and complicated. Its annual incidence ranges from 3 to 7 per 100.000 person-years. Although relatively rare, it can cause significant morbidity and mortality if unrecognized and treated (4-6). The Gram-positive cocci such as the *Staphylococcus*, *Streptococcus*, and *Enterococcus* species are accounted for 80-90% of overall. *Staphylococcus aureus* is a leading cause of IE cases in many regions of the world (5-9). The modified Duke criteria were recommended for diagnostic classification. These criteria are based on clinical, echocardiographic and biological findings, as well as the results of blood cultures, serologies, and other imaging techniques (4,10). Echocardiography is the most

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important imaging such that transesophageal echocardiography (TEE) is superior to transthoracic echocardiography (TTE) for absolute diagnosis. Multislice computed tomography (CT), radiolabeled leukocyte scintigraphy or ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scanning, magnetic resonance imaging (MRI) are the auxiliary imaging techniques for demonstrating specific complications (7,11-14). Pathogen-specific recommendations for antibiotics are complex and are well summarized in recent guidelines. Optimal therapy of IE requires high dose IV bactericidal antibiotics for a prolonged period. Valvular surgery should be considered for the specific patient group (4,10,12).

William Osler said "Few diseases present greater difficulties in the way of diagnosis than malignant endocarditis, difficulties that in many cases are practically insurmountable." while describing IE as "malignant endocarditis" (15). Because the serious chaos environment in the emergency room, an emergency physician should always be aware of recognizing IE among the relevant patient groups. Therefore, we are aiming to present the clinical features and course of IE patients in a tertiary-care university hospital emergency department (ED).

METHODS

This descriptive retrospective single center study was conducted at the ED of a university hospital by scanning patients' data between January 1, 2010 and December 31, 2019. Patient data were obtained by scanning the hospital automation program (ISHOP) related diagnostic codes with acute and subacute endocarditis, and those were re-evaluated according to the modified Duke criteria and included in the study. Patients aged over 18 years and diagnosed with definite IE or possible IE according to the modified DUKE criteria were enrolled in the study. Patients who were re-diagnosed or re admitted in 6 months after their first episodes were included in the study as a different case. The Clinical Researches Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Ethical Board approved this study based on retrospective design by approval number 31887016-804.01-195972.

The data about the participants were obtained from the ISHOP system and the Ministry of Health Death Electronic Registration System. Age, gender, comorbid conditions (previous IE, congenital heart disease, valvular heart disease, malignancy, immunosuppressive conditions, and dialysis), predisposing factors (presence of catheter, IV drug use, dental procedure) were recorded for each patient. Symptoms at the first admission to the ED, fever, pulse, blood pressure, respiratory rate, oxygen saturation, Glasgow Coma score, and laboratory results were evaluated as baseline variables. Transthoracic and TEE findings of all participants in the study were obtained and the ejection fraction and affected valve were recorded. Additionally, PET/CT and cardiac MRI were also used in patients with an indication. Microbiological data were obtained from blood culture results. In the clinical course, IE-related embolic events, acute renal failure, congestive heart failure, abscess and metastatic infections and surgical intervention were evaluated as complications and added to the study. Length of stay and in-hospital mortality are variables that determine the clinical outcome.

Statistical Analysis

Data statistics were performed using IBM SPSS Statistics 21 for the Windows program. Descriptive results are given by mean and standard deviation for continuous variables. Categorical data are shown by the number of observations and frequency (n, %). The suitability of the data to the normal distribution was evaluated with the Shapiro-Wilk test. Chi-square tests are used to compare categorical variables. Mann-Whitney U test was used to compare two groups. $P<0.005$ value was accepted as significant.

RESULTS

Twenty-nine patients were included in the study who were detected with the specified diagnostic codes in computerized health record system. Twenty patients (69%) were admitted with definite IE, and 9 patients (31%) met just possible IE diagnosis according to modified Duke's criteria. Mortality was seen in 5 (17%) patients due to IE and related complications. The mean age of the patients was 56.3±18.8 years and it ranges between 19 and 89. 41% of the patients are women and there is no significant difference in gender between patients who died and survived. Acquired valvular disease was noted in 19 (66%) IE patients. In the following, immunosuppressive conditions (24%) and malignancy (21%) are other important risk factors. Non-specific symptoms like fever (76%), fatigue (69%), dyspnea (38%), palpitation (34%), and chest pain (17%) are reported as the initial complaints in ED. A cardiac murmur was the most common physical examination finding in our study. Mean body temperature and respiratory rate were significantly higher in non-survivors than in survivors (Table 1). There is no significant difference between non-survivors and survivors for laboratory results such as white blood count, platelet, C-reactive protein, total bilirubin, erythrocytes sedimentation rate and lactate levels (Table 1).

Twenty-one patients had significant blood culture results according to modified Duke's major criteria. *S. aureus* subspecies,

Table 1. Initial characteristics of IE patients in emergency department				
	All patients n=29	**Survivors n=24**	**Non-survivors n=5**	**p**
Age, mean ± SD (min-max)	56.3±18.8 (19-89)	54.8±19.4 (19-89)	63.6±15.0 (48-82)	0.352
Characteristics, n (%)				
IE according to Duke' criteria	29	24 (83%)	5 (17%)	-
Definite	20 (69%)	16 (67%)	4 (80%)	
Possible	9 (31%)	8 (33%)	1 (20%)	
Gender, n (%)				
Male	17 (59%)	13 (54%)	4 (80%)	0.370
Female	12 (41%)	11 (46%)	1 (20%)	
Comorbidities and risk factors, n (%)				
Acquired valvular heart disease	19 (66%)	15 (63%)	4 (80%)	0.633
Immunsupression	7 (24%)	5 (21%)	2 (40%)	
Malignity	6 (21%)	4 (16%)	2 (40%)	
Previous IE history	3 (10%)	3 (13%)	0 (0%)	
IV drug use	3 (10%)	3 (13%)	0 (0%)	
Presence of catheter	3 (10%)	1 (4%)	2 (40%)	
Hemodialysis	3 (10%)	1 (4%)	2 (40%)	
Dental procedure	3 (10%)	2 (8%)	1 (20%)	
Congenital heart disease	1 (3%)	1 (4%)	0 (0%)	
Initial symptoms, n (%)				
Fever	22 (76%)	18 (75%)	4 (80%)	1.000
Fatigue	20 (69%)	18 (90%)	2 (40%)	0.287
Dyspnea	11 (38%)	8 (33%)	3 (60%)	0.339
Palpitation	10 (34%)	8 (33%)	2 (40%)	0.339
Chest pain	5 (17%)	5 (21%)	0 (0%)	-
Physical examination, n (%)				
Murmur	23 (79%)	19 (79%)	4 (80%)	1.000
Purpura	5 (17%)	4 (17%)	1 (20%)	
Other signs	1 (4%)	0 (0%)	1 (20%)	
Vital signs, mean ± SD				
Body temperature	37.8±9.5	37.6±8.8	38.8±7.8	0.016
Systolic blood pressure	119.2±18.6	118.4±16.3	122.8±29.4	0.758
Diastolic blood pressure	72.3±10.4	71.2±9.7	77.2±13.3	0.352
Heart rate	98.2±20.8	97.7±21.3	100.6±20.2	0.556
Oxygen saturation	95.4±2.7	95.6±2.9	94.4±1.5	0.201
Respiratory rate	20.3±2.8	19.8±2.7	22.8±2.3	0.037
GCS	14.7±0.6	15 (0)	14.2±1.3	0.382
Laboratory results, mean ± SD				
White blood cells ($x10^3/mm^3$)	9.0±3.7	9.2±3.6	7.7±5.2	0.594
Platelets ($x10^5/mm^3$)	2.0±1.4	2.0±1.3	2.0±0.2	0.801
C-reactive protein	226.5±52.9	224±56.3	240.3±21.9	0.222
Total bilirubin	2.1±1.2	1.3±1.0	1.5±1.1	0.352
Erythrocytes sedimentation rate, mean ± SD				
1st hour	62.8±27.8	62.3±27.1	66.0±39.3	0.663
2nd hour	100.2±33.2	102.1±32.5	86.6±17.6	0.606
Lactate	5.0±1.9	5.7±2.0	1.6±0.6	0.900

IE: Infective endocarditis, GCS: Glasgow Coma score, SD: Standard deviation, IV: Intravenous, min: Minimum, max: Maximum

Streptococci and *Enterococci* were the prominent species in the blood culture results. Beside microbiological evidence, 25 of the patients (86%) showed significant echocardiographic findings as well. Mitral valve and aortic valves were the most affected parts of the endocardial surface in our study. In 8 patients (28%) echocardiographic evidence was detected on both mitral and aortic valve. Separately, mitral valve and aortic valves were affected in 6 (21%) and 5 (17%) patients, respectively. The right side of the heart was infected in 6 (20%) patients associated with tricuspid valve and implantable devices. All died patients (100%) had remarkable echocardiographic evidence; however, just 69% of survivors had significant findings on TEE or TTE examination (Table 2).

Considering the Duke's minor criteria; fever was recorded in 76% of patients and predisposing heart factors were seen in 59%.

Table 2. Diagnostic characteristics of IE patients according to modified Duke's criteria

Characteristics	All patients n=29	Survivors n=24	Non-survivors n=5	p
Significant blood culture for IE	21 (72%)	16 (67%)	5 (100%)	**0.016**
MSSA	9 (31%)	7 (29%)	2 (40%)	
MRSA	3 (10%)	2 (8.3%)	1 (20%)	
Streptococci	4 (14%)	3 (13%)	1 (20%)	
Enterococci	5 (17%)	4 (17%)	1 (20%)	
Candida albicans	1 (3%)	1 (4%)	0 (0%)	
Not detected	8 (28%)	8 (100%)	0 (0%)	
Significant ECHO findings for IE	25 (86%)	20 (83%)	5 (100%)	**0.003**
Mitral valve	6 (21%)	4 (17%)	2 (40%)	
Aortic valve	5 (17%)	4 (17%)	1 (20%)	
Tricuspid valve	3 (10%)	2 (8%)	1 (20%)	
Mitral + aortic valve	8 (28%)	7 (29%)	1 (20%)	
Implantable devices	3 (10%)	3 (13%)	0 (0%)	
PET/CT	3 (10%)	3 (13%)	0 (0%)	
Cardiac CT	4 (14%)	3 (13%)	1 (20%)	
Predisposing heart conditions	17 (59%)	14 (58%)	3 (60%)	1.000
Fever	22 (76%)	18 (75%)	4(80%)	1.000
Immunological signs	1 (3%)	1 (4%)	0 (0%)	-
Vascular phenomena	5 (17%)	4 (17%)	1 (20%)	-
Other microbiological evidences	6 (20%)	6 (21%)	0 (0%)	-

IE: Infective endocarditis, MSSA: Methicillin-susceptible *Staphylococcus aureus*, MRSA: Methicillin-resistant *Staphylococcus aureus*, ECHO: Echocardiography, PET/CT: Positron emission tomography/computed tomography

Minor microbiological findings that are inadequate for Duke's major criteria (20%), vascular phenomena (17%), immunological signs (3%) were the other criteria that our patients had met for IE (Table 2).

IE related complications such as embolic events, akut kidney injury, congestive heart failure, metastatic abcess and spondylitis were observed in 14 (48%) patients. Gentamicin added cefazolin or amoxicillin and gentamicin added vancomycin combinations were the most preferred antibiotic regimens in our study. Median day of their antbiotherapy duration was the same, 28 days for both. Thirteen patients had undergone surgery due to IE related severe valve failure and 12 of those were survived after surgery. The mean length of stay in the hospital for all patients was 30.5±14.7 days. Survived patients stayed significantly longer than non-survivals, and the mean length of hospital stay of non-survivors and survivors was 34.1±13.2 and 13.4±8.5 days, respectively (Table 3). In univariable regression analysis, body temperature had a significant odds ratio for in-hospital mortality (p=0.040, 95% confidence interval, odds ratio: 1.120) (Table 4).

DISCUSSION

Clinical presentation of the IE is polymorphic, variable and symptoms are non-specific (13). Peripheral and more typical signs, such as Osler nodes, Janeway lesions, Roth spots, are quite rare and seen at the late stage in subacute forms (15). Difficulties and challenges of the IE diagnostic results in delaying the rapid antibiotic therapy. This study may lead the emergency room doctors to be aware of the potetinal IE patients.

Totally 411.716 over 18 years old patients were admitted to the ED in ten years. Ten-years-incidence of our department is 7-8/100,000 and this incidence rate is a bit more than ESC and AHA guidelines (4-6). Male gender was dominant in our study population (59%). Mean age of the patients was 56.3 years and interestingly, Leblebicioglu et al. (16) reported the mean age of the IE patients in Turkey as 45.2 years in 2006. In this point, our results are similar to those of Northern Europe and France sourced IE reviews' (17,18). A growing number of the elderly population and decreasing of the pediatric rheumatic valve disease incidence in Turkey can be the reasons for this transition to the elder age group of the IE patients (19,20).

Predisposing heart diseases are a prominent risk factors in this presented study and as well as recent other studies. IE was previously more often related to rheumatic heart disease in younger patients, but it is now is more frequent in older patients, and the number of associated risk factors is increasing. Malignity, immunodeficiency diseases and related treatments

Table 3. Compliacation, surgery, antibiotherapy and length of hospital stay rates of patients				
	All patients n=29	**Survivors n=24**	**Non-survivors n=5**	**p**
Complications	14 (48%)	12 (50%)	2 (40%)	-
Embolic events	5 (17%)	4 (17%)	1 (20%)	-
Acute kidney injury	6 (21%)	5 (21%)	1 (20%)	-
Congestive heart failure	1 (3%)	1 (4%)	0 (0%)	-
Abcess	1 (3%)	1 (4%)	0 (0%)	-
Spondylitis	1 (3%)	1 (4%)	0 (0%)	
Antibiotic regimen n (%)				
Cefazolin or amoxicillin + gentamicin	10 (34%)	9 (38%)	1 (20%)	-
Vancomycin + gentamicin	10 (34%)	9 (38%)	1 (20%)	-
Daptomysin, only	6 (20%)	4 (16%)	2 (40%)	-
Daptomysin + rifampin	1 (3%)	1 (4%)	0 (0%)	-
Daptomysin + PIP + TAZO	1 (3%)	0 (0%)	1 (20%)	-
Vancomycin, only	1 (3%)	1 (4%)	0 (0%)	-
Antibiotherapy duration, day (median, IQR)				
Cefazolin or amoxicillin + gentamicin	28.0 (19.0)	28.0 (19.0)	2.0	-
Vancomycin + gentamicin	28.0 (25.0)	28.0 (25.0)	12.0	-
Daptomysin only	28.0 (12.5)	28.0 (12.75)	7.5	-
Daptomysin + rifampin	42.0	42.0	-	-
Daptomysin + PIP + TAZO	18.0	-	18.0	-
Vancomycin, only	21.0	21.0		-
Surgery	13 (45%)	12 (50%)	1 (20%)	-
Length of hospital stay	30.5±14.7	34.1±13.2	13.4±8.5	**0.002**
PIP + TAZO: Piperacillin + tazobactam, IQR: Interquartile range				

Table 4. Univariate and multivariate regression analyses for mortality				
Risk factors	**Univariate analyse**		**Multivariate analyse**	
	OR (95% CI)	**p value**	**OR (95% CI)**	**p value**
Body temperature	1.120	0.040	-	0.210
Respiratory rate	-	0.054	-	-
Significant blood culture	-	0.999	-	-
Significant ECHO findings	-	0.999	-	-
Length o stay in hospital	0.812	0.032	-	0.426
CI: Confidence interval, OR: Odds ratio, ECHO: Echocardiography				

make the patients vulnerable to persistent infections. Therefore, cancer and immunodeficiency are the other major causes of IE (4-6,21). Presence of catheter and routine hemodialysis and the increasing proportion of the IE etiology. Especially central line associated bacteremia in chronic renal disease patients mostly transforms to the infectious endocardial surface (17,18). Asgeirsson et al. (17) revealed that IV drug using is the most common specific underlying conditions in *S. aureus* associated IE. Only three patients have an IV drug using history however IV drug use is another growing risk factor for IE (21,22).

Most common symptom and physical examination findings are fever and heart murmur just as reported in previous studies (4,6,22). Other clinical features are fatigue, dyspnea and palpitation in the first sight in the ED. According to our results, measured body temperature and breath rate are significantly higher in deads. Just inflammation markers, which are C-reactive proteins and erythrocyte sedimentation rate excessively higher than the cut-off value and other considered laboratory findings do not affect the mortality. Our results are in coherent with Şimşek-Yavuz et al.'s (23) that they reported no significant difference in white blood cell counts, creatinine, C-reactive protein, and erythrocyte sedimentation rate between deads and survivors however only blood thrombocyte counts were signifiacantly higher in dead IE patients.

Staphylococcus aureus bacteremia (SAB) incidence has been increasing because of older population age, hemodyalisis, IV drug using and consecutive interventional process. For those

who with SAB face a risk of IE whether immunocompromised or not. Current guidelines express that *S. aureus* is the most frequent microbiological cause of IE. Furthermore, *S. aureus* caused IE has a worse prognosis than other IE forms associated microorganisms (17,24). In this presented study, *S. aureus* was reproduced in 41% % of the significant blood cultures, which is higher than Şimşek-Yavuz et al. (23) and Vahabi et al.'s (22) findings. We did not detect any coagulase-negative *Staphylococcus* but in overall 68% of the significant blood culture for IE was Gram-positive coccus, which includes *Streptococci* and *Enterococci* as well. 28% of the cases considered as culture-negative endocarditis who diagnosed with echocardiographic evidence and other minor criteria of Duke. Fungal IE prevalence changes between 1 and 10 % of all IE cases. *Candida* spp. are isolated in 53-68% of fungal endocarditis with *C. albicans* is the most common (25). We observed that one surviving patient with implantable cardioverter-defibrillator had *C. albicans* associated IE. Brucella endocarditis is rare but Brucellosis is endemic in the Mediterrannean and the Middle East (26). Brucella endocarditis was not reported in this study. This might be the reason for this result that the decreased consumption of unpasteurized milk in city centers in Turkey.

Transeosopahageal and TTE both were performed for each patient in our study and diagnostic evidence for IE was found in 86%. ^{18}F-FDG PET/CT was performed for 3 (10%) patients. A total of 4 (13%) underwent contrasted thorax CT to detect IE complications such as metastatic abscesses and rule out pulmonary embolism for symptomatic individuals. According to previous studies, those imaging technics reveals that mitral and aortic valves, either seperately or both are mostly affected part of heart (4,10). However, tricuspid valve and implantable device infection, which means the right side endocarditis rate is totally 20% in this presented study and approximately as same as Zencirkiran Agus et al.'s (27) results.

Recent studies show that the mortality rate for IE is approximately 20% within the first 30 days, though exact rates vary between population-based studies (28). According to our study, 5 (17%) patients died from IE and related complications. Embolic events had the highest frequency among the other complications, such as acute kidney injury, CCF, metastatic abscesses and spondylitis. Embolic complications more often affected the neurologic system such that in some cases we diagnosed IE through cerebrovascular embolism-related symptoms. Multiple studies have expressed the benefit of appropriate timing for surgery to decrease morbidity and mortality in selected patients (28). Our findings also support previous studies that overall 13 patients (45%) in this study underwent valve surgery due of severe valve regurgitation related IE and only one patient died after surgical intervention. Average duration in the hospital of the patients in this study is 30.5±14.7 days that which is little shorter than Şimşek-Yavuz et al.'s (23) results (36.59±22.79 days), nevertheless survivors stayed significantly longer than died patients in the hospital in both studies.

Study Limitations

Infected endocarditis research in the literature were conducted as large multicenter studies. We designed this study with patients who were diagnosed in the ED of a single center; therefore, the study population remains smaller than other similar studies in the literature.

CONCLUSION

IE may occur in all age groups and manifest with varied symptoms. Emergency physicians should consider IE in patients with fever and predispose heart conditions. *S. aureus* subspecies have the highest frequency, mitral and aortic valves either seperately or both are mostly affected part of the heart. IE related complications may change the course of the disease. Surgical intervention reduces the mortality rate so that it is beneficial for selected patients.

Ethics

Ethics Committee Approval: The Clinical Researches Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Ethical Board approved this study based on retrospective design by approval number 31887016-804.01-195972.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: F.Ç., T.D., S.Ö., A.Y., S.B., A.İ., İ.İ., Design: F.Ç., T.D., S.Ö., A.Y., İ.İ., Data Collection or Processing: F.Ç., T.D., S.B., A.İ., İ.İ., Analysis or Interpretation: F.Ç., T.D., S.Ö., A.İ., Literature Search: F.Ç., T.D., S.Ö., A.Y., S.B., A.İ., İ.İ., Writing: F.Ç., T.D., S.Ö., A.Y.

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