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Infective Endocarditis – An Observational Study

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ABSTRACT

Introduction: Despite all the progresses made in the management of infectious and cardiovascular diseases, the incidence of infective endocarditis remains high.

Aim: the assessment of etiological, clinical, therapeutic aspects in patients with endocarditis.

Material and method: A retrospective observational study in 40 patients with infective endocarditis was conducted, over a period of 5 years. Parameters related to demographic, risk factors, clinical aspects, nature and location of valve damage, bacteriological and therapeutic parameters were assessed. Echocardiography was used to confirm the location of the endocarditis; the aetiology of the disease was identified through the isolation of bacteria from blood cultures by using an automatic BacT/ALERT® system.

Results: Patients' age ranged between 31 – 84 years old. The disease was present predominantly in male patients (67.5%). 70% of the patients were positively diagnosed with endocarditis and 30% with possible endocarditis; the most frequent localization was the native valves in 75% of the cases, compared to the localization in the prosthetic valves, 25%; the aortic valve was involved in 60% of the cases, mitral valve in 40% of the patients.

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Aetiology of endocarditis was confirmed in 55% of cases as follows: *Enterococcus faecalis*, *speciae*, *Staphylococcus epidermidis*, *Escherichia coli*, *Streptococcus gallolyticus*, coagulase-positive methicillin resistant *Staphylococcus aureus*, coagulase-positive methicillin sensitive *Staphylococcus aureus*, *Staphylococcus lugdunensis*, coagulase-negative staphylococci, *Streptococcus gordonii*, *viridans*, *agalactiae*.

Antibiotic treatment was administered according to the antibiogram in 55% of the cases.

Conclusions: *Staphylococcus speciae* was the most frequent etiologic agent both in case of native and prosthetic valve endocarditis, with aortic valve predominance.

Keywords: endocarditis, diagnosis, aetiology, treatment, complications

Introduction

Infective endocarditis (IE) is a systemic peculiar disease, not uniform, with various different forms (linked to the initial clinical manifestation, the underlying cardiac disease, the microbiological findings, the presence or absence of complications, and patient characteristics); typical lesion is the vegetation localized to the vascular endothelium.

IE affects particularly the heart valves, which leads to local destruction, followed by regurgitation. The annual incidence is estimated at 3-9 cases IE /100,000 people, the gender ratio is 2:1 male/female [1,2,3,4]. Risk factors related to IE are age, pre-existing degenerative valvular lesions, presence of a prosthetic valve or a prosthetic material used for cardiac valve repair, previous IE, some congenital heart diseases (without or with surgical repair) hemodialysis, co-morbidities such as diabetes, human immunodeficiency virus infection, intravenous drug use [5, 6, 7, 8].

Complications of IE include heart failure, uncontrolled infection, embolism, acute renal failure, myocarditis, pericarditis, splenic abscess, rheumatic complications. Heart failure appears after acute regurgitation provoked by valve destruction (mitral chordal rupture, leaflet rupture or perforation, interference of the vegetation mass with leaflet closure). Uncontrolled infection encompasses persisting infection, perivalvular extension or infections related to resistant microorganisms. Stroke is a severe embolic complication of left-sided IE; in native right-sided and pacemaker lead IE pulmonary embolism appears frequently; embolic events may occur in 20-50% of patients [5, 9, 10].

Infective endocarditis diagnosis is based on clinical features, echocardiographic identification of vegetation and microbiological diagnosis (blood cultures, histological, molecular biology techniques) [10]. Transthoracic echocardiography (TTE) correlated with transesophageal echocardiography (ETE) identifies the presence of vegetation in 90% of cases, valvular regurgitation in 60% of cases, paravalvular abscesses in 20%, and rarely dehiscence and fistulae [5, 7, 8].

In the past infective endocarditis was known as a disease of young adults with rheumatic valve disease; currently it affects older patients, mainly due to the increased number of invasive diagnostic procedures (prosthetic valves, pacemakers, etc.) [5,12,13].

Objectives

The purpose of this study was to assess clinical, etiologic, therapeutic parameters, complications and outcome of patients with infective endocarditis.

Material and Methods

The study was conducted on 40 patients diagnosed with IE according to Duke criteria, admitted to the Infectious Diseases Clinic (tertiary care hospital) over a period of 5 years (January 1st, 2010 to December 31, 2014). Were evaluated: socio-demographic parameters, clinical features (presence of infectious syndrome, dyspnoea, fatigue, pallor, heart auscultation changes, hepatosplenomegaly, etc.), biological constants (WBC – white blood cell counts, ESR – erythrocyte sedimentation rate, fibrinogen, CRP – C reactive protein). The existence of co-morbidities and risk factors was followed, as well as post-therapy disease course and complications.

Localization and identification of vegetation was performed using transthoracic and transesophageal echocardiography.

Blood cultures were collected on aerobic and anaerobic culture media, taking into account the fact that a high number of patients were pretreated with antibiotics before admission. Blood cultures were processed using an automated method (BacT/ALERT® Automatic system, bioMérieux Inc, USA).

Statistical analysis was performed using the MedCalc Software, version 12.5.0.0. Data were considered as nominal or quantitative variables. Nominal variables were characterized using frequencies. A chi-square test was used in order to compare the frequencies of nominal variables. The level of statistical significance was set at $p < 0.05$.

Ethical considerations the study has been performed in the accordance with standards of the

Declaration of Helsinki. Written informed consent was obtained from each patient.

Results

In our study there was a higher incidence of IE in the 57-67 years age group (19 cases- 47.5%) compared to age groups of 30-56 years (13 cases - 32.5%) and over 68 years (8 patients - 20%). The gender distribution showed a predominance of male IE patients (27 cases - 67.5%) compared to females (13 cases - 32.5%). The patients studied were from rural areas (21 patients - 52.5%) and urban areas (19 patients - 47.5%).

Clinical manifestations suggestive of infective endocarditis were identified at admission of the patients as follows: infectious syndrome (35 patients - 87.5%); septic cutaneous metastases (6 patients-15% of cases). Hepatosplenomegaly was present in 19 patients (47.5% of cases); asthenia, fatigue, effort related dyspnoea, anorexia were reported by all patients.

Auscultation changes were found in 26 patients (65%) as follows: holosystolic murmur in the mitral area (16 patients-40%); diastolic murmur in the left parasternal area (10 patients -25%).

Laboratory tests showed the presence of anaemia in 30 patients (75% cases). Acute phase reactants had elevated values in 100% of cases (WBC average value of 13,000/mm³ with predominance of neutrophils and left-side deviation of the white blood cell formula, ESR average value: 73.23 mm/h, fibrinogen average value: 506.4 mg/dl, CRP average value: 51.04 mg/l).

Pre-existing conditions known to patients and reported at hospitalization were: mitral valve prolapse in 20 patients (50%); degenerative aortic disease - 13 patients (32.5%); presence of prosthetic valves 10 patients (25%); type 2 diabetes - 8 patients (20% of cases).

The diagnosis of IE was established according to Duke's criteria; 70% of patients were diagnosed

with certain endocarditis, 30% of cases with possible endocarditis.

Identification and localization of vegetation was achieved by TTE and TEE examinations, and thus structures located on native valves were identified in 75% (30 patients), and on prosthetic valves in 25% (10 patients). The most affected native valve was the aortic valve in 20 patients (50% of the cases), as compared to the mitral valve (10 patients, 25% of the cases). In case of prosthetic valves, the lesions were equally present both on the aortic and the mitral position in 12.5% of cases. With regard to the type of valve, 8 patients had mechanical valves and 2 patients had biological valves (Figure 1).

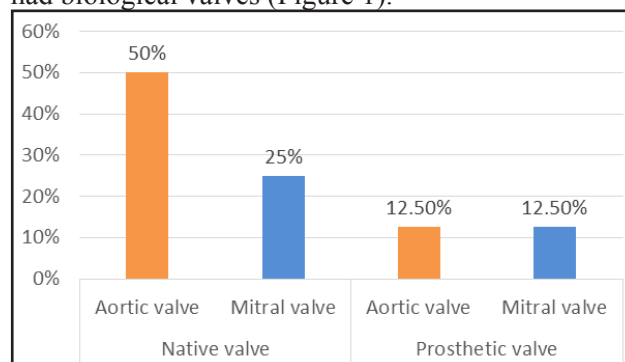


Figure 1 - Localization of vegetation

The etiology of endocarditis was confirmed in 22 (55%) patients with positive blood cultures collected before the initiation of antibacterial therapy. Negative bacteriological results of blood cultures were found in 18 patients (45%) (Figure 2).

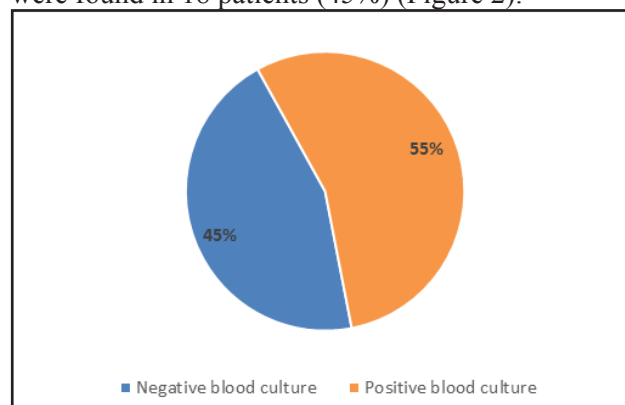


Figure 2 – Patients' distribution regarding results of blood cultures

Bacterial agents identified from blood cultures were the following: *Enterococcus faecalis* (4 patients – 10.0%); *Enterococcus* species (3 patients – 7.5%), *Staphylococcus epidermidis* - MRSA (3 patients – 7.5%), *E. coli* (2 patients -5.0%); *Streptococcus gallolyticus* (2 patients - 5.0%); coagulase-positive methicillin resistant *Staphylococcus aureus* - MRSA (2 patients – 5.0%); coagulase-positive methicillin sensitive *Staphylococcus aureus* - MSSA (1 patient – 2.5%), *Staphylococcus lugdunensis* - MRSA (1 patient – 2.5%), coagulase-negative *Staphylococcus aureus* -CoNS (1 patient – 2.5%); *Streptococcus gordonii* (1 patient – 2.5%); *Streptococcus viridans* (1 patient – 2.5%); *Streptococcus agalactiae* (1 patient – 2.5%); blood cultures were negative in 18 patients (45%) (Table I).

Table I – Etiological agents identified from blood cultures

	Pts (nr.)	Pts (%)
<i>Enterococcus faecalis</i>	4	10.0%
<i>Enterococcus speciae</i>	3	7.5%
<i>Staphylococcus epidermidis</i> - MRSA	3	7.5%
<i>Escherichia coli</i>	2	5.0%
Methicillin resistant <i>Staphylococcus aureus</i> MRSA	2	5.0%
<i>Streptococcus gallolyticus</i>	2	5.0%
Methicillin sensitive <i>Staphylococcus aureus</i> - MSSA	1	2.5%
<i>Staphylococcus lugdunensis</i> - MRSA	1	2.5%
Coagulase negative staphylococci - CoNS	1	2.5%
<i>Streptococcus gordonii</i>	1	2.5%
<i>Streptococcus viridans</i>	1	2.5%
<i>Streptococcus agalactiae</i>	1	2.5%
Negative	18	45.0%
TOTAL	40	100%

Patients – Pts

In patients with prosthetic valve IE, the etiological agents were *Enterococcus faecalis* (1 patient), *Staphylococcus epidermidis* (1 patient), *E. coli* (1 patient), coagulase negative staphylococci – CoNS (1 patient).

Conditions that predisposed patients to bacteraemia before to the diagnosis of IE and etiologic agents that were identified in 22 cases (55%) are the following: invasive procedures (2 patients with central venous catheters, urinary catheters in 3 patients, cholecystectomy-2 patients). In these cases onset of the disease was less than 60 days after the procedure; the involved etiologic agents were: coagulase positive *Staphylococcus aureus* (MRSA), *Enterococcus* spp., *E. coli*.

In patients who underwent dental procedures, the etiologic agent was *Streptococcus viridans*, and the onset of IE was 60 days after the dental intervention (1 patient). In patients who had respiratory infections (12 patients), skin infections (2 patients) the identified etiologic agents were Gram-positive cocci, and the onset of IE was less than 60 days from the intercurrent.

Initial antibiotic treatment was administered empirically, and subsequently it was according to the sensitivity of the isolated etiologic agent. In cases where the etiological agent was not identified in blood cultures (18 patients-45%), treatment in native and prosthetic valves IE, consisted of the combination of vancomycin (30 mg/kg/day intravenously iv in 2 doses) + gentamycin (3mg/kg/day iv in 2 doses) + ciprofloxacin (400 mg/day iv in 2 doses). In cases of IE with MRSA the treatment consisted of the vancomycin (30 mg/kg/day iv in 2 doses) + gentamycin (3mg/kg/day iv in 2 doses) combination; in case of MSSA etiology, the antibiotic combination used was oxacillin (100 mg/kg/day iv in 3 doses) + gentamycin (3mg/kg/day iv. in 2 doses) ; in case of *Enterococcus* spp. and *faecalis* etiology, patients received treatment with vancomycin (30 mg/kg/day iv. in 2 doses) + gentamycin (3mg/kg/day iv in 2 doses). In case of IE with *Streptococcus viridans*, *agalactiae* and *gallolyticus* the combination consisted of penicilline G (12million U/day iv. in 4 doses) + gentamycin (3mg/kg/day iv. in 2 doses); and in patients with IE with *E. coli* the treatment was meropenem (3g./day iv. in 3 doses) + gentamycin (3mg/kg/day iv. in 2 doses). Antibacterial treatment was performed over a period of 4-6 weeks depending on the course of the disease. In case of patients who have developed complications, early surgical intervention was recommended.

Hemodynamic complications were: heart failure (28 patients – 70% of the cases); mitral (22 patients – 55% of the cases) and aortic regurgitation (16 patients – 40%) were significantly present ($p=0.001$, respectively $p=0.02$). Periannular abscesses (7 patients, 17.5% of the cases) were diagnosed in aortic valve localization. 5 patients (12.5%) developed rupture of mitral chords. We diagnosed cerebral embolism in 7 patients (17.5%) with IE at the aortic valve level. (Figure 3).

Surgery was required in 70% of patients. The number of deaths in the study group was low (3 patients-7.5% of the cases).

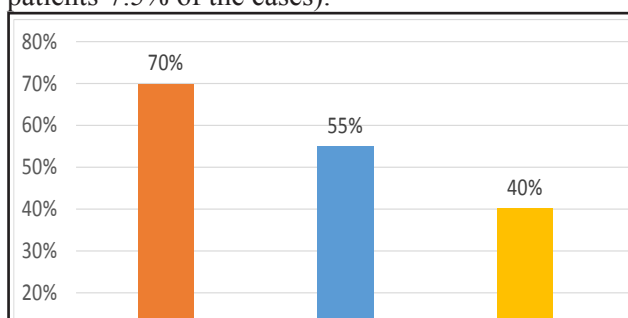


Figure 3 - Hemodynamic and structural complications

Discussions

Despite all the progress in infectious diseases and cardiovascular diseases, the incidence of IE is comparable to the pre-antibiotic era (15-30 patients/1 million people/year). In our study there was a higher incidence of IE in the 57-67 years age group (19 cases, 47.5%) compared to other age groups. Similarly, in other studies, as a consequence of changes in the population at risk for IE, the average age of patients increased gradually from 30 - 40 years old in the pre-antibiotic and initial antibiotic era to 47 - 64 years old in recent decades. [14].

In case of native valve IE, the most frequently involved valves are: mitral valve in 45-55% of the cases, aortic valve in 35-40%, and tricuspid valve in 18-20%. Approximately 15% of patients may have

simultaneous aortic and mitral valve involvement [15].

The incidence of IE on valvular prostheses is increasing to 30% of the cases.

The risk of developing IE on prosthetic valves is 1% in the first 12 months, and 20-30% in the first 60 months following surgery.

In our study, the most frequently involved native valve was the aortic valve in 20 patients -50% of the cases, compared to the mitral valve (10 patients-25% of cases). In case of prosthetic valves, lesions were equally present both in the aortic valve and the mitral valve, 12.5% of the cases.

The underlying conditions known so far in patients and reported at hospitalization are predominantly concerned with mitral valve prolapse (20 patients-50% of the cases); followed by degenerative aortic disease (13 patients-32.5% of the cases); prostheses (10 patients -25% of the cases). Similarly, in other studies, mitral valve prolapse is the predominant structural cardiac abnormality that predisposes IE, and represents 7-30% of native valve IE in adults who are not intravenous drug users or have not suffered from nosocomial infections.

In the study group *Staphylococcus aureus* was the etiologic agent involved in the etiology of IE in eight patients and 20% of the cases; other studies have found a frequency of 22%, followed by *Streptococcus* spp. [16]. In our study six strains of methicillin-resistant *Staphylococcus aureus* were isolated, four out of which were community strains and only two of them nosocomial. Studies report that more than 90% of coagulase positive and negative staphylococci are resistant to penicillin. Methicillin-resistant strains are resistant to all beta-lactam antibiotics, but remain susceptible to vancomycin. Although staphylococci are destroyed by antibiotics that act on the cell wall, bactericidal effects of these agents may be potentiated by aminoglycosides. Our study patients benefited also from these potent synergistic combinations.

Streptococcus gallolyticus is responsible for 5-19% of the EI cases, being an etiologic agent frequently involved in patients with neoplastic diseases of the colon. The aortic valve is more often involved, followed by the mitral valve; in our study *Streptococcus gallolyticus* was isolated in two patients (5% of cases), where IE was localized at the

level of the native aortic valve.

In order to establish certain diagnosis of IE and to identify and localize the vegetation transthoracic and transesophageal echocardiography examination are required [17]. Sensitivity to transthoracic echocardiography is around 60% and the specificity for vegetation is 90%. Transthoracic echocardiography is essential for diagnosing IE when the source of bacteremia is unknown, but also for its complications; a negative result does not exclude the diagnosis of endocarditis [14,15].

In our study IE was diagnosed in 92.5% of patients using transthoracic and transesophageal echocardiography. Additionally, diagnosis was also based on other parameters such as acute phase reactants (ESR, fibrinogen, CRP) which had elevated values in all patients, infection associated anaemia and left deviation of the white blood cell formula with predominance of segmented granulocytes. Anemia generally worsens with the increase in duration of the disease, and consequently, according to some authors, it may be absent in acute IE; in our study it was detected at the time of diagnosis.

An important feature of the study was the high number of patients (25 patients, 62.5% of the cases), who developed IE localized at the level of native and prosthetic aortic valves.

Blood cultures identified the etiologic agent in 55% of the cases, whereas other studies reported positivity of up to 90% [13]. High frequency of negative blood cultures in our study (45% of cases) is probably due to antibiotic treatment of patients before sample collection for etiologic agent identification.

Systemic embolisms (lung, spleen, brain) typically occur in 25-30% of the patients with IE. In our study we observed just cerebral embolism in 16.2% of cases. Tendinous chord ruptures were found in five patients (12.5%) ($p=0.01$) whereas vegetation were localized on the mitral valve, compared to the same injury to the aortic valve - (one patient - 4.2%); in these cases *Staphylococcus aureus* was the etiologic agent. Periannular abscesses were identified in seven patients (17.5%) ($p=0.01$), with lesions more often localized to the aortic valve than the mitral valve, where this complication was not found ($p=0.006$).

The disease course of patients who received both empiric antibiotic treatment, and according

to bacterial susceptibility, was slowly favourable. Surgery was required in 70% of the patients. According to studies, cardiac surgery plays an important role in the treatment of patients with cardiac complications of IE. Data suggest that the mortality rates are unacceptably high when patients with such complications are treated only with antibiotics, while mortality rate is reduced when antibiotic treatment is combined with surgery.

Fatality in the study group was 7.5% compared to the incidence of death cases reported in the literature 18-20% for community acquired endocarditis, and 25-50% of nosocomial endocarditis [11,14,15,18].

Conclusions

Infective endocarditis in the study group involved middle aged patients, and it was predominant in males. The etiology of acute endocarditis was dominated by *Staphylococcus* spp, with a higher frequency of methicillin-resistant community strains.

The aortic valve was most commonly affected, compared to other locations. Native valve involvement was predominant in comparison to valvular prostheses.

Surgery was required in most patients, and its beneficial effects were demonstrated. Fatality rate was low.

Acknowledgements

The authors have nothing to disclose. No competing financial interests exist.

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