Study of infective endocarditis in Alexandria main university hospitals

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Received 7 November 2012; accepted 11 January 2013  
Available online 13 March 2013

Abstract  Objectives: To describe the incidence, clinical characteristics, microbiological profile and in-hospital outcome of infective endocarditis (IE) in our center.  
Methods: A prospective study that was conducted on 50 consecutive patients admitted to our cardiology department diagnosed as Duke definite IE. The study was conducted for a period of one year and started on the 1st of September 2009 till the end of August 2010. All patients were subjected to detailed history taking, clinical examination, blood culture and echocardiography.  
Results: The study was carried out on 29 males (58%) and 21 females (42%) with a mean age of 33 years. The mean duration of delay from onset of symptoms till diagnosis was 54 days. Native valve endocarditis was found in 34 patients (68%). Blood cultures were positive in 27 patients (54%). Staphylococci were the prevalent microorganisms (52%). In-hospital events included: heart failure in 29 patients (58%), systemic embolization in 13 patients (26%), para-valvular abscess in 8 patients (16%), septic pulmonary emboli in 7 patients (14%), dehiscence of prosthetic valves in 5 patients (10%) and renal failure in 2 patients (4%). Surgical intervention was indicated in 41 patients (82%). Only 16 patients (39%) had early surgical intervention. In-hospital mortality was 22%. However, the mortality rate improved in the patients who had undergone early surgical intervention (18.75% versus 32%).  
Conclusions: Infective endocarditis remains a major health problem. It carries high in-hospital events with a high mortality rate. Delayed diagnosis of the disease and culture negative IE are common. Staphylococci are the prevalent microorganisms. Early surgical intervention improves survival.

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1. Introduction

Infective endocarditis (IE) is a non-contagious infection of the lining of the heart chambers and heart valves, caused by bacteria, fungi, or other infectious agents. IE is a peculiar disease for at least three reasons. First, neither the incidence nor the mortality of the disease has decreased in the past 30 years.
Secondly, IE presents in a variety of different forms. For this reason, IE requires a collaborative approach, involving primary care physicians, cardiologists, surgeons, microbiologists, infectious disease specialists, and frequently others, including neurologists, neurosurgeons, radiologists, and pathologists. The incidence of IE ranges from one country to another within 3–10 episodes/100,000 persons per year. A recent systematic review of 15 population-based investigations accounting for 2371 IE cases from seven developed countries (Denmark, France, Italy, The Netherlands, Sweden, the UK, and the USA) showed an increasing incidence of IE associated with a prosthetic valve, an increase in cases with underlying mitral valve prolapse, and a decrease in those with underlying rheumatic heart disease. The epidemiology, clinical and microbiologic spectra of IE is significantly different in the developing countries compared to the western world. These differences can be attributable to multiple factors present in poorer countries including: significantly higher incidences of rheumatic heart disease and uncorrected congenital heart disease, excessive and improper use of antibiotics, late clinical presentation, and worse outcomes. In addition, developing countries may have a higher incidence of culture negative endocarditis than in the western world, largely secondary to prior doctor-prescribed or self administered antibiotic use. Life-threatening complications from IE are still common despite echocardiographic diagnosis and the use of effective antibiotics.

Several exciting developments offer the prospect of improved prevention and treatment of IE. Vaccines targeted at specific bacterial adhesions may inhibit valve colonization, and newer antibacterial agents with novel effects may attenuate the invasive properties of virulent organisms such as Staph aureus. Finally, modified biomaterials in development may reduce the risk of IE in patients with artificial heart valves or other intra-cardiac prosthetic material. At the end, despite these advances, the diagnosis and management of IE remain a considerable challenge across the range of medical disciplines.

The main aims of our study are to prospectively describe the incidence, clinical characteristics, microbiological profile and in-hospital outcome of infective endocarditis in our center.

2. Methods

This is a prospective study that was conducted on 50 patients admitted to our cardiology department diagnosed as Duke definite infective endocarditis. The study was conducted for a period of one year and started on the 1st of September 2009 till end of August 2010. Exclusion criteria included: patients who proved to have any source of infection other than IE and those with clinical suspicion of IE who could not be categorized as definite IE according to the guidelines on the prevention, diagnosis and treatment of Infective Endocarditis of the European society of Cardiology (ESC).

Structured data collection sheet was used to record the data, it included: I- Questionnaire on: demographic data, clinical presentation at admission, duration of symptoms, prior use of antibiotics, diagnosis delay and in-hospital course and outcome. II- Clinical features: new cardiac murmurs or manifestation of heart failure, peripheral signs of IE (e.g. Osler’s nodes, Janeway lesions, and splinter hemorrhages.), clubbing of the nails, splenomegaly, and complications related to systemic embolization: (e.g. neurological manifestation, pulmonary embolization, and peripheral ischemia). III- Laboratory data: complete blood picture, renal functions, liver transaminases, ESR, CRP and Blood cultures: Ten ml of blood was collected for blood culture under strict aseptic technique, to be added directly to a Signal blood culture bottle (Oxoid) (a system that employs a single bottle capable of supporting the growth of both aerobic and anaerobic bacteria). Three sets were obtained with a time interval of at least one hour in-between and within a maximum of 48 h. All bottles were incubated for a total period of 21 days. Positive blood cultures were subjected to: Gram and Ziehl-Neelsen stained smears. Subcultures were made onto blood agar, (Columbia agar base supplemented with 5% defibrinated blood, Oxoid), Chocolate agar and MacConkey’s agar. The plates were incubated for 24 h in a 5% enriched CO2 at 37 °C both aerobically and anaerobically. Subcultures were also made on Sabouraud dextrose agar slopes (Oxoid) incubated at 30 °C for at least 2 weeks (for possible fungal etiology). Bacterial identification was performed according to standard microbiological procedures (Gram stained films, catalase and coagulase tests, growth on bile esculin medium, sensitivity to bacitracin and optochin, sugar fermentation, pattern of growth on triple sugar iron, testing for oxidase, urease, citrate and indole, amino acid decarboxylation and motility). Routine antibiotic sensitivity testing was done by the disk diffusion method (Oxoid) according to guidelines of the Clinical Laboratory Standards Institute (CLSI).

IV- Radiological examination: chest X-ray was done for all patients in this study. Other imaging modalities were done when indicated in some cases: CT of brain or MRI if presented with neurological symptoms, CT of chest if pulmonary septic emboli were suspect, U/S abdomen or even CT of abdomen was done whenever abdominal organ embolization is suspected and Duplex ultrasound was performed in the case of suspected ischemic extremities due to embolization. V-Echocardiographic examination: transthoracic echocardiography (TTE) examinations were performed on all patients using the Envisor-CHD, Philips echocardiography machine. Transesophageal echocardiography (TEE) was performed in 27 patients using Omiplane-III probe. Images were recorded in digital loop display format. Both studies focused on: (Calculation of the left ventricular ejection fraction (EF), site, size, number and mobility of the vegetations, the presence of valvular damage and/or regurgitation, intra-cardiac abscesses, prosthetic valve dehiscence, para-valvular leakage and intra-cardiac fistula).

2.1. Statistical analyses

After data entry into a specially designed sheet using Microsoft Excel, a printout of the data was thoroughly revised. Then the file was transferred into Statistical Package for Social Science (SPSS, Chicago, IL, USA) version 17 formats. Normality test was performed and as most of the variables resulted in insignificant Kolmogorov–Smirnov which indicates that the variables were considered to be normally distributed and were dealt with using parametric statistics. Scale variables were compared using independent Student’s t test, while categorical data were compared using the Chi square test. Repeated measures were compared using the paired t test. Sensitivity analysis was presented using the Chi square test. Repeated measures were compared using the paired t test. Sensitivity analysis was
carried out using ROC curve statistics. The study adopted a 0.05 level of significance (alpha error) and beta error was set to be 20%.

3. Results

3.1. Demographic data

Fifty consecutive patients were included in this prospective study. All patients were diagnosed to suffer from definite infective endocarditis based on the modified Duke criteria. Two of our patients gave history of prior IE one year before their recent admission. The first one had a recurrence on top of an intra-cardiac device and the second one on top of an aortic prosthesis. There were 29 males (58%) and 21 females (42%) while the age of studied patients ranged between 16 and 78 years with a mean age of 33.42 ± 11.37 years.

3.2. Diagnosis delay

The mean time from symptom onset to diagnosis was relatively long. The diagnosis delay ranged between 4 days and 210.0 days with a mean of 54.62 ± 49.75. Diagnosis delay less than 30 days was encountered in 32% of the studied patients while, 42% had diagnosis delay that ranged between 30 and 60 days, 14% had diagnosis delay that ranged between 61 and 90 days and 12% were diagnosed after 90 days from the onset of illness. The distribution of the studied cases according to the duration of diagnosis delay is shown in fig. 1.

3.3. Referral Sites of the patients

The patients were referred to our department from multiple different referral sites; 17 patients (34%) from internists, 13 patients (26%) presented in the emergency department with unsettled diagnosis, 8 patients (16%) were referred from cardiologist outpatient clinics, while 5 IE cases (10%) were referred from private hospitals and 4 patients (8%) from public hospitals and three patients (6%) from the internal medicine department in our university hospital.

3.4. Clinical characteristics

Based upon the modified Duke’s criteria, 27 patients (54%) had two major criteria and 23 patients (46%) had 1 major + 3 minor criteria. All our patients (100%) had fever with the temperature ranging between 38 and 40°C followed by dyspnea grade (III–IV) in 29 patients (58%). Neurological deficits were reported in 7 patients (14%), hemiparesis occurred in 5 of them; one case had TIA (transit ischemic attack), and the last case suffered from low back pain complicated by paraplegia; Magnetic resonant imaging of that patient revealed a vertebral septic lesion. During the initial physical examination, cardiac murmurs were heard in 40 patients (80%).

3.5. Extra-cardiac manifestations

Beside the embolic neurological complications previously mentioned, splenomegaly was found in 9 patients (18%), 4 of them (8%) had splenic infarction. Pulmonary embolization was diagnosed in 7 patients (14%); 6 of them had right sided IE secondary to intravenous drug abusers (IVDA). Peripheral arterial embolisation was found in 2 patients (4%). Two patients (4%) had renal impairment necessitating dialysis Fig. 2.

3.6. Presumed source of infection

The majority of cases; 27 patients (54%) were admitted without definite presumed source. IE secondary to intravenous drug abuse (IVDA) was detected in 13 patients (26%). The history of preceding dental interventions was recorded in only 4 patients (8%). History of gastrointestinal (GIT) or Genitourinary (GU) procedures before IE was mentioned in 3 patients (6%). Cardiac catheter-related bacteremia was seen in 2 patients (4%) and one case (2%) had a history of prior surgery (appendicectomy) Fig. 3.

3.7. Preexisting cardiac disease

Twenty-eight patients (56%) had preexisting cardiac disease, while 22 patients (44%) did not show a preexisting cardiac lesion. Thirteen out of the 22 patients were IVDAs while the remaining nine patients showed structurally normal hearts. The natures of the preexisting cardiac diseases among our studied patients were demonstrated in Table 1.

3.8. Type s of IE according to the localization of infection and the presence or absence of intra-cardiac materials

The left side of the heart alone was involved in 30 patients (60%); 18 patients (36%) had the disease on the left side

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**Figure 1** The percentage of patients according to the duration of diagnosis delay in days.

**Figure 2** Showing the distribution of the cases according to the clinical presentation.
native valves; 11 patients (22%) had the disease on top of left sided prosthesis and one patient (2%) with hypertrophic obstructive cardiomyopathy (HOCM) showed the vegetation on the interventricular septum. The mitral valve was affected in 14 patients (28%), 7 on native mitral valves and an equal number on top of mitral valve prosthesis. The aortic valve was involved in 10 cases (20%), 8 on native aortic valves and 2 on aortic valve prosthesis. Both mitral and aortic valves were affected in 5 patients (10%); combined native mitral and aortic valves infections were encountered in 3 patients while the other 2 patients had a double prosthesis IE.

The right side of the heart alone was involved in 16 patients (32%). The tricuspid valve alone was affected in 11 patients (22%) of right sided IE while the pulmonary valve was affected in one IVDA case (2.0%). One case (2%) had IE on the right side of VSD (outlet type) (2.0%). Intra-cardiac devices IE were diagnosed in the remaining 3 patients (6.0%).

Combined right and left sided (IE) was diagnosed in 3 patients (6%). Extra cardiac IE was diagnosed on top of the conduit graft from pulmonary trunk to the right ventricle in a case with transposition of the great arteries (TGA) (2 %). Surgical procedure was done 6 years before IE had occurred.

The distribution of the studied patients according to the localization of infection is summarized in Table 2.

### 3.9. Blood cultures

A single positive blood culture was discarded for establishing the diagnosis of IE for the possibility of potential contaminants. According to the yield of the blood cultures, our results were divided into two groups: negative blood culture in 23 patients (46%) and positive blood culture in 27 patients (54%).

### 3.10. Negative Blood cultures

Culture-negative endocarditis (CNE) was defined as endocarditis with failure to identify the organism following inoculation of at least three independent blood samples in a standard blood culture system with negative cultures after at least seven days of incubation and subculturing. Blood cultures were negative in 23 patients (46%). Seventeen patients (73.9%) out of the 23 CNE gave history of the prior use of antibiotics, while 5 patients (21.7%) with negative blood cultures did not receive antibiotics. In one patient (4.3%) the issue of prior use of antibiotics was not certain.

### 3.11. Positive Blood cultures

Blood cultures were positive in 27 patients (54%). Gram-positive bacteria were the prevailing organisms representing 81.48% of positive blood cultures (22 isolates). Staphylococci were isolated in 14 patients (51.8%) followed by streptococci in 8 patients (29.6%). Gram –negative bacilli were isolated in only 4 patients (14.8%). These included 2 Pseudomonas, 1 Klebsiella and 1 E-coli isolates. Candida spp. was isolated in only one case. Table 3.

### 3.12. Echocardiography examination

Transthoracic echocardiography (TTE) was performed in all our cases. Vegetations were detected by TTE in 40 patients (80%). Left ventricular ejection fraction (EF) ranged from 40.0 to 85.0% with a mean of 61.68 ± 9.05%. Transesophageal echocardiography (TEE) was indicated in 27 patients; 13 patients with native valve endocarditis, all patients with prosthetic valve endocarditis ($n = 11$) and 3 cases with IE complicating pacemaker devices. Vegetations were presented in 41 patients (82%) of all cases both by TTE & TEE. Intra-cardiac abscesses were detected in 9 patients (18%); six of them were aortic root abscesses, two were mitral annular abscess and one inside the right ventricle in relation to an infected pace

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**Table 1** Distribution of the patients according to preexisting cardiac disease.

<table>
<thead>
<tr>
<th>Preexisting cardiac diseases</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous valve surgery</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Early prosthetic valve IE</td>
<td>4</td>
<td>8.0</td>
</tr>
<tr>
<td>Late prosthetic valve IE</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>RHD</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>4</td>
<td>8.0</td>
</tr>
<tr>
<td>CTGA</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>VSD</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>Subaortic membrane</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>Bicuspid aortic valve</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>Intra cardiac devices</td>
<td>3</td>
<td>6.0</td>
</tr>
<tr>
<td>MVP with MR</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>HOCM</td>
<td>1</td>
<td>2.0</td>
</tr>
</tbody>
</table>


---

**Table 2** Distribution of cases according to the localization of infection.

<table>
<thead>
<tr>
<th>Side</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left sided IE</td>
<td>30</td>
<td>60.0</td>
</tr>
<tr>
<td>Native</td>
<td>19</td>
<td>38.0</td>
</tr>
<tr>
<td>Prosthesis</td>
<td>11</td>
<td>22.0</td>
</tr>
<tr>
<td>Right sided IE</td>
<td>16</td>
<td>32.0</td>
</tr>
<tr>
<td>Left and right sided IE</td>
<td>3</td>
<td>6.0</td>
</tr>
<tr>
<td>Intra-cardiac device Related</td>
<td>3</td>
<td>6.0</td>
</tr>
<tr>
<td>Extra-cardiac device Related</td>
<td>1</td>
<td>2.0</td>
</tr>
</tbody>
</table>
Table 3 Microbiology profile in the culture positive group.

<table>
<thead>
<tr>
<th>Identified microorganism</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococci</td>
<td>14</td>
<td>51.8</td>
</tr>
<tr>
<td>Coagulase negative</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Coagulase positive</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>methicillin sensitive</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Coagulase positive</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>methicillin resistant (MRSA)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Streptococci</td>
<td>8</td>
<td>29.6</td>
</tr>
<tr>
<td>Alpha-hemolytic streptococci</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Non hemolytic streptococci</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Gram negative bacilli</td>
<td>4</td>
<td>14.8</td>
</tr>
<tr>
<td>Fungi: Candida</td>
<td>1</td>
<td>3.7</td>
</tr>
</tbody>
</table>

maker lead. Extension of infection to the aortic-mitral fibrosa was encountered in two patients. The all echocardiographic data are summarized in Table 4.

Fig. 4 demonstrated different varieties of echocardiographic finding in a sample of studied cases.

3.13. Other Radiological examinations

Ultra sound abdomen: revealed splenic infarction in four patients. CT brain: revealed embolic brain infarctions in seven patients. Two more patients suffered from subarachnoid hemorrhage. MRI showed an extra dural ring –enhancing lesion (abscess) measuring about 1 cm indenting the left antro-lateral aspect of the thecal sac and compromising the related nerve roots at the level of LV2-3 and LV4 in one case.

3.14. Major complications and in-hospital mortality

Advanced heart failure, NYHA functional class III-IV: Heart failure represented the most frequent complication among our studied patients. Heart failure occurred in 29 patients (58%). The leading cause of heart failure was valvular insufficiency. Left sided heart failure secondary to native valvular regurgitation was encountered in 14 patients. Seven patients had tricuspid valve regurgitation and right sided heart failure. Three patients had combined left and right sided valves regurgitation and presented with biventricular failure. Five patients had left sided prosthetic valves dehiscence and peri-valvular regurgitation. Systemic and pulmonary Embolization: Systemic embolization occurred in 13 IE patients (26%). No hemorrhagic strokes occurred in 6 patients. Four patients suffered from splenic infarction and 2 patients had peripheral arterial embolization. One patient presented with septic embolic focus in the vertebral. Pulmonary emboli were diagnosed in 7 patients (14%) with right sided IE secondary to IVDAs. The risk of embolism was related to the size and mobility of the vegetations. This relation is shown in Table 5 Peri-annular complications: extension of the infection and intra-cardiac abscesses were detected by TEE in 9 patients. Prosthetic valves’ dehiscence was detected in 5 patients. Renal failure requiring dialysis: two patients suffered from acute renal failure that necessitated dialysis, their serum creatinin was 2.3 and 2.9 mg/dl. One of those patients died during his hospital stay. Intracranial hemorrhage: Two patients died from intracranial hemorrhage. Septic shock: Two patients developed fulminant sepsis and they were mechanically ventilated and died from septic shock.

3.15. In-hospital mortality

Eleven patients (22%) died during their hospital stay. The leading causes of death were: three patients died postoperatively, two from heart failure, two from intracranial hemorrhage, two from septic shock, one from renal failure and another one from non-hemorrhagic stroke. Eight (72.7%) of the dead patients had positive blood cultures. The isolated organisms were staphylococci (4 cases), gram-negative bacilli (2 cases), with fungal infection in one and streptococci in another one. Diagnosis delay ranged between 4 days and 210 days with a mean of 54.62 ± 49.75. This delay had a direct impact on the mortality. Delayed diagnosis was associated with increased mortality rate as seen in Table 6.

3.16. Surgical treatment

For all patients, management including indication for surgery was based upon the latest ESC guidelines for the management of infective endocarditis13. Nine patients (18%) were assigned for medical treatment and they responded favorably. Surgery was indicated in 41 patients (82%). However, it was performed in only 16 patients (32%). The other twenty-five patients did not receive surgical management (50%). The mortality rate was high in the later group compared to those who underwent surgical intervention (32% versus 18.75%). Most patients had more than one indication for surgery. Congestive heart failure and large vegetations were the main indications for surgical intervention. The indications of surgical treatment and mortality according to surgery status are summarized in Table 7.

3.17. Study results concerning the mode of acquisition

Community acquired infection occurred in 32 patients (64%), followed IVDAs in 13 patients (26%) , then health care associated IE in 5 patients (10%) following balloon mitral
valvuloplasty, cardiac catheterization and neglected central catheters (10%).

3.18. Microbiological profile based on the mode of acquisition

Community acquired IE (32 patients): blood cultures were positive in 17 patients (53.1%). Staphylococci were isolated in 9 patients (52.9% of the identified organisms in this subgroup), followed by streptococci identified in 7 patients (41.2%) and gram negative bacilli were isolated in one patient (5.8%). Fungi were not isolated in this subgroup.

Intravenous drugs abuse IE (13 patients): blood cultures were positive in five cases (38.5%). Staphylococci were isolated in 2 patients (40% of the identified organisms in this subgroup). Gram-negative bacilli were isolated in another 2 patients (40%). Candida was isolated in one patient (20%).

Health care associated IE (5 patients): blood cultures were positive in all the five cases (100%). Staphylococci were isolated in three patients (60% of the identified organisms in this subgroup). Streptococci were isolated in one patient (20%). Gram-negative bacilli were isolated in another patient (20%).

Table 5 The distribution of the embolic events regarding the size of vegetations.

<table>
<thead>
<tr>
<th>Size of vegetations</th>
<th>No of embolic events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥15 mm</td>
<td>10 (20)</td>
</tr>
<tr>
<td>&gt;10 and ≤15 mm</td>
<td>5 (10)</td>
</tr>
<tr>
<td>≤10 mm</td>
<td>4 (8)</td>
</tr>
<tr>
<td>No vegetations (abscess)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Table 6 The relation between in-hospital mortality and diagnosis delay.

<table>
<thead>
<tr>
<th>Duration in days</th>
<th>No. of patients</th>
<th>No. of death</th>
<th>*Mortality rate</th>
<th>MCp</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>16</td>
<td>2</td>
<td>12.5</td>
<td>0.722</td>
</tr>
<tr>
<td>30–60</td>
<td>21</td>
<td>6</td>
<td>28.57%</td>
<td></td>
</tr>
<tr>
<td>61–90</td>
<td>7</td>
<td>2</td>
<td>28.57%</td>
<td></td>
</tr>
<tr>
<td>&gt;90</td>
<td>6</td>
<td>1</td>
<td>16.66%</td>
<td></td>
</tr>
</tbody>
</table>

MCp: p value for Monte Carlo test,*percentage was calculated from the diagnosed patients in each duration.
IE and its predisposing risk factors have changed over time with the emergence of IVDA; intravascular prostheses, nosocomial exposure, hemodialysis, and age-related valvular sclerosis which are more prevalent than rheumatic heart disease, especially in the developed countries. Our study was carried on all cases of IE admitted to the cardiology department of the Alexandria main university hospital during a one-year period. We did not exclude any cases diagnosed as Duke-definite IE and the total number of cases during this year was 50 patients.

4.1. Demographic data

The present study showed a higher incidence of IE in males (58%) than in females (42%) with a ratio of 1.4:1. This is comparable to what was reported by Beynon RP et al.10 in which he stated that the male: female ratio is 2:1. Tariq M. et al.11 also found that the male: female ratio was 1.8:1.

The mean age in our study was 33.42 ± 11.37 years as similar to what was found in most studies in developing countries. Ullah et al.12 found that most of the patients belong to the younger age group, with almost 90% falling below 40 years. Majority of the researchers from developing countries report a similar age group affected, including Rehman S et al.13 and Tariq M et al.11 Also, Koegelenberg et al.14 found that patients with definite endocarditis had a mean age of (37.7 years) and in Kaser-Elini study by Al-Mogheer et al.15 the mean age was (32 ± 13 years). In developed countries Hill et al.16 mentioned that more than one-half of all IE cases in the United States and Europe occur in patients over the age of 60 years, and the median age of patients has increased steadily during the past 40 years. This trend is probably due to two factors: the decline in the incidence and importance of rheumatic heart disease as a risk factor for IE and the increasing proportion of elderly subjects in the general population who are more likely both to develop degenerative valve disease and to require valve replacement, which is associated with an increased risk of IE. While Wilson LE et al.17 said that IE is now more often observed in new at-risk groups in industrialized countries, including IVDA (mean age 30–40 years) and adults, including elderly individuals (>65 years) with valve prostheses or chronic healthcare-associated conditions. (This means that patients with chronic health conditions are associated with frequent hospitalization and intravenous drug therapy e.g. chronic renal failure, long term insertion of central lines, cancer patients on regular chemotherapy cycles).

4.2. Diagnosis delay

Diagnosis delay in the present study ranged from 4 to 210 days with the mean of 54.62 days while the median was 40 days; in Kaser Elini the mean was 65 ± 96 days15 near to our diagnosis delay. Van Le et-al.18 in the study of serious complications after IE found that the range to diagnosis was 0–103 days; this also reported by Hasbun et al.19 The median diagnostic delay for IE in our study was 40 days while Hill et al showed the median time between the onset of symptoms and the diagnosis of IE was 8 days.16 The prolonged time of diagnosis delay may be due to; decreased awareness of the treating physicians and general practitioners of the disease and the importance of early diagnosis, symptomatic treatment of fever without searching for underlying etiologies and the empirical use of self prescriptions of antibiotics by Egyptian patients and even pharmacists as well.

4.3. Presumed source of infection

The majority of cases in the present study; 54% were admitted without definite presumed source of infection, on the other hand no definite source of bacteremia was identified in 71.8% of IE patients studied by Adrian C et al.20 Followed by IVDA; 26% of our studied patients, while Frontera JA et-al.21 reported that the incidence of IE among IVDA is believed to be 100–1000 times. In our study dental procedure was recorded in 8% of patients similar to what was reported in the 2007 American Heart Association (AHA) guidelines, in a series of 17 IE cases 8% that had dental interventions within 3 months before IE diagnosis.22 Also 8% of IE patients in the present study had previous procedures (6%), genitourinary procedures and 2% anorectal procedures, this is near to the incidence which was reported in the same AHA guidelines, as in a series of 20 cases (9%) that had invasive anorectal and genitourinary procedures. In the current study, catheter induced IE was reported in 2 patients (4%) of IE cases; one case after percutaneous mitral balloon valvotomy (2%) and the other cases (2%) had coronary angiography in rheumatic heart disease (RHD) before valve replacement surgery. Al-Aghbari et al.23 reported one case with IE post percutaneous mitral balloon valvotomy.

4.4. Pre-existing cardiac disease

In the current study 18% had no underlying cardiac disorder or were from IVDAs group. In a French study 47% of patients with IE presented without previous history of any underlying cardiac disorder.24 In our study, the incidence of RHD within IE cases was 16% nearly similar to studies from Hong Kong and Thailand that found RHD in 18% and 12% of cases, respectively.25 While a study from Singapore,26 mentioned RHD in only 4% of IE cases also Marjion et al.27 found that the prevalence of IE in RHD was 2.2 per 1000. This difference between those studies may be due to increase in the prevalence of RHD in developing countries.

During the last 20 years, only 33 cases of IE complicated hypertrophic cardiomyopathy (HCM) were published.28 IE complicating HCM is not commonly reported but occurs almost universally in patients showing evidence of outflow tract obstruction. In our study, only one patient (2%) had IE on top of HCM with outflow obstructive to be concordant to many studies. The estimated cumulative 10-year probability of

### Table 7 Distribution of the studied cases according to the indications of surgery.

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<tr>
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<tr>
<td>Heart failure</td>
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</tr>
<tr>
<td>Large size of vegetation ≥15 mm</td>
<td>20</td>
<td>40.0</td>
</tr>
<tr>
<td>Embolic event*</td>
<td>13</td>
<td>26.0</td>
</tr>
<tr>
<td>Peri-annular complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abscess</td>
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<td>16.0</td>
</tr>
<tr>
<td>Dehiscence</td>
<td>5</td>
<td>10.0</td>
</tr>
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<td>4</td>
<td>8.0</td>
</tr>
<tr>
<td>Pacemaker related abscess</td>
<td>1</td>
<td>2.0</td>
</tr>
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</tr>
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Diagnosis delay in the present study ranged from 4 to 210 days with the mean of 54.62 days while the median was 40 days; in Kaser Elini the mean was 65 ± 96 days near to our diagnosis delay. Van Le et-al.18 in the study of serious complications after IE found that the range to diagnosis was 0–103 days; this also reported by Hasbun et al.19 The median diagnostic delay for IE in our study was 40 days while Hill et al showed the median time between the onset of symptoms and the diagnosis of IE was 8 days.16 The prolonged time of diagnosis delay may be due to; decreased awareness of the treating physicians and general practitioners of the disease and the importance of early diagnosis, symptomatic treatment of fever without searching for underlying etiologies and the empirical use of self prescriptions of antibiotics by Egyptian patients and even pharmacists as well.

The majority of cases in the present study; 54% were admitted without definite presumed source of infection, on the other hand no definite source of bacteremia was identified in 71.8% of IE patients studied by Adrian C et al.20 Followed by IVDA; 26% of our studied patients, while Frontera JA et-al.21 reported that the incidence of IE among IVDA is believed to be 100–1000 times. In our study dental procedure was recorded in 8% of patients similar to what was reported in the 2007 American Heart Association (AHA) guidelines, in a series of 17 IE cases 8% that had dental interventions within 3 months before IE diagnosis.22 Also 8% of IE patients in the present study had previous procedures (6%), genitourinary procedures and 2% anorectal procedures, this is near to the incidence which was reported in the same AHA guidelines, as in a series of 20 cases (9%) that had invasive anorectal and genitourinary procedures. In the current study, catheter induced IE was reported in 2 patients (4%) of IE cases; one case after percutaneous mitral balloon valvotomy (2%) and the other cases (2%) had coronary angiography in rheumatic heart disease (RHD) before valve replacement surgery. Al-Aghbari et al.23 reported one case with IE post percutaneous mitral balloon valvotomy.

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developing IE in obstructive HCM is <5%. In the most comprehensive study of prevalence and incidence, Spirito et al.\textsuperscript{28} identified 10 patients with HCM and endocarditis, outflow tract obstruction and atrial dilatation present in all cases. In our present study, PVE was reported in 22% of all cases of IE, similar to Rivas P et al.\textsuperscript{29} who reported that the IE developing on prosthetic valves accounts for 15–32% of all cases of IE, and in Kaser-Elini study prosthetic valves account for 20.6% of all cases.\textsuperscript{15}

As regards intra cardiac devices, in our study 6% of all IE cases is in agreement with the reported rate of infection ranging from 0.13% to 19.9% for permanent pacemakers (PPMs) and from 0.7% to 1.2% for intra-cardiac defibrillators (ICDs).\textsuperscript{30}

The relative incidence of IE in congenital heart disease (CHD) had increased because of improved survival with CHD. CHD with IE was reported in 8% of the studied cases, on the other hand Rathor et al.\textsuperscript{32} in the retrospective study of IE, reported that the incidence of IE in CHD was 2.2%. While Tariq M et al.\textsuperscript{1} found that 31% of IE patients had underlying CHD. The differences between studies may be related to the variation in the use of antimicrobial prophylaxis before different procedures and the proper early identification of the CHD cases.

The current study showed that only 2% had MVP with mitral regurgitation, near to the incidence recorded by Al -Aghbabi et al.\textsuperscript{23} in Yemen as the MVP in their studied cases was recorded in 2.8% only. Steckelberg JM et al.\textsuperscript{33} reported that the risk of IE per 100,000 patient-years was 4.6 in patients with MVP without an audible cardiac murmur and 52 in patients with MVP with an audible murmur of mitral regurgitation.

4.5. Blood cultures

In the current study, 46% of patients were found to have negative blood culture. This finding is consistent with other studies from developing countries.\textsuperscript{34,35} However, Krcmary et al.\textsuperscript{34} and Omezzine-Letaief\textsuperscript{35} from developed countries have also reported similar percentages of culture negative cases. While comparing with other studies, Chen CH et al.\textsuperscript{36} reports 5.2%, Zamorano J et al.\textsuperscript{37} 8.7% and in the USA, ‘culture negative’ endocarditis constitutes only 2.5–30% of all IE diagnosed cases.\textsuperscript{38} This low culture positivity/high culture negativity is understandable as most patients in our country like other underdeveloped countries receive unjustified antibiotics prior to admission in hospital, while consulting area doctors or even pharmacists. Similarly, in this study, a significant association is seen between previous intake of antibiotics and culture negative endocarditis.

Positive blood culture is a major diagnostic criterion for IE. Blood cultures were positive in our study in 54% while ESC reported that the positive blood culture is the most important category, representing 85% of all IE. Failure to culture the organism in IE may result from inadequate anti microbial technique, infection with highly fastidious bacteria or non bacterial organism or most importantly, from the administration of antimicrobial agents before blood cultures are obtained.\textsuperscript{12}

The organisms found in the present study are as follows: Staphylococcus group was found in 14 patients (51.85%), streptococcus group in 8 patients (29.63%), Gram-negative bacilli 4 cases (14.82%) and fungi in 3.7%. Koegelenberg et al.\textsuperscript{14} reported the positive blood cultures in\textsuperscript{23} patients yielded the following organisms: viridans streptococci in 6 patients (28.6%), pneumococci in 2 patients (9.5%), group D streptococcus in 1 patient (4.8%), other streptococci in 2 patients (9.5%), staphylococci in 3 patients (14.3%), and 18.2% of Gram-negative bacilli. In our result MRSA endocarditis occurred in 6% of our patients in agreement of the study done in Lebanon where MRSA endocarditis occurred in 7% of all cases.\textsuperscript{39}

4.6. TTE versus TEE findings

Over the last 20 years, the use of echocardiography has been instrumental in confirming the diagnosis of endocarditis. In one study, reviewing 534 consecutive requests for TTE to exclude IE, vegetations were found in only 4%.\textsuperscript{40} Thus, although good quality TTE may exclude the diagnosis in patients at low risk, a negative study does not exclude IE or its complications if these are strongly suspected. In our results TTE was performed in all cases of IE patients 50 (100%) and TEE in 27 patients (54%). TTE was positive in 40 subjects (80%) that were in agreement with Nashmi A et al.\textsuperscript{41} who reported that TTE showed vegetations in 37 patients (72.5%). In our study, TEE were done in 27 patients, 10 cases (20%) with negative TTE confirmed to be positive by TEE and the other 17 cases were positive by TTE and reconfirmed by TEE; thus the result was positive in all cases subjected to TEE (100%) which was similar to what was reported by Nashmi A et al.\textsuperscript{41} who mentioned that the TEE detected vegetation in 14 patients (27.7%) in whom TTE was negative or questionable. On the other hand, Evangelista A et al.\textsuperscript{42} reported that; for the detection of vegetations; TEE has a sensitivity of 90–100%, whereas that of TTE ranges from 40% to 63%. They also reported that; vegetation size also affects TTE sensitivity since only 25% of vegetations <5 mm and 70% of those between 6 and 10 mm were identified.

5. IE reported complications

5.1. Heart failure

Heart failure (HF) is the most frequent complication of IE and represents the most frequent indication for surgery in such cases.\textsuperscript{43} Valve destruction causing acute regurgitation is the most characteristic lesion leading to HF in native valve IE.\textsuperscript{9} In our study HF presented in 58% of the studied cases. Van Le et al reported that HF was secondary to valvular insufficiency due to IE in 9% of the studied cases.\textsuperscript{44}

5.2. Periannular complications

Extension of IE beyond the valve annulus is associated with increased mortality, development of HF, and a higher likelihood of surgery. In the current study; abscesses was recorded in 18% of the patients, and 44% of abscesses were detected by TEE. These results were Similar to Anguera et al.\textsuperscript{45} who reported that Intra-cardiac abscesses occur in approximately 10% to 40% of cases of IE. In PVE the predominant complications are peri-prosthetic leaks and dehiscence.\textsuperscript{46} In our study the para-valvular leak was recorded in 50% of patients with PVE (5 cases); on the other hand; David et al.\textsuperscript{47} found that 34.1% of patients with PVE had evidence of a prosthetic valve...
complication such as dehiscence or new para-valvular regurgitation. The higher incidence of complications in our patients with PVE could be related to the aggressiveness of infection, delayed diagnosis and the early improper inefficient antibiotic prescriptions.

5.3. Embolic event

Dislodgements of part of vegetations of infected tissue or intra-cardiac thrombi may cause embolic events, the most common complication during IE. Embolic events are a frequent and life-threatening complication of IE related to the migration of cardiac vegetations. In our research we found that 26% of IE cases presented with different sites due to systemic embolization and this was comparable to Mocchegiani R et al. who found that embolization occurs in 22–50% of cases of IE. ESC also reported that embolic risk is very high in IE, with embolic events occurring in 20–50% of patients, 12% of them to the spleen leading to splenic infarction associated with splenomegaly. While Anguera et al. considered it as a rare complication that develops by bacteraemic seeding of a mild infarction or due to the occlusion of splenic artery by embolized vegetations, or it may follow an infected embolization. Splenic infarction in our study presented in 4 cases (8%). In our study of extremities distal embolization was recorded in 4% of the cases; 2% of them to the lower limb and 2% to the upper limb. While Habib et al. found the incidence of extremities distal embolization was 13%. Those differences between studies as regards distal embolization to the spleen or to the extremities could be attributed to the difference in the duration of studies and vegetation size. In our present study 14% had pulmonary embolization and the highest incidence was with IVDA as 71.5% of pulmonary embolization occurred with IVDA. In agreement with Mathew et al. and Ruotsalainen et al. who mentioned that right-sided IE frequently causes pulmonary embolization that occurred in 40–75% of drug addicts who have tricuspid valve endocarditis.

5.4. Intracranial hemorrhage

The patients recorded as having intracranial hemorrhage in the present study were only 2 (4%). Sonneville et al. reported that the intracranial hemorrhage accounts for 12–30% of neurologic complications of IE and even 29% of all neurologic complications in critically ill patients with IE.

5.5. Renal failure

Decreased renal function at the time of hospitalization with IE is an important prognostic indicator of a poor outcome. In our study 2 patients (4%) were complicated by renal failure in agreement with AL-Aghbari et al. who documented renal failure in 2 patients which represented 2.7% of his studied cohort. Miyake et al. also reported one case of renal failure that developed as an initial manifestation of IE.

5.6. In-hospital mortality

In our result the in hospital mortality rate was 22% near the retrospective cohort study in Turkey which was done by Erbuy et al. the in-hospital mortality was 38.7% and the majority was due to CHF. On the other hand in the studied conducted by Fedeli et al. the in-hospital mortality was low, only 14%. The difference between our study and the results of other studies may be attributed to a small number of patients who underwent early surgical treatment also those with delayed presentations with well-established complications. Recently a large multicenter study showed that early surgery was associated with a decreased risk of both in-hospital and late mortality.

7. Treatment

Successful treatment of patients with IE relies on microbial eradication by antimicrobial drugs and decreasing the risk of systemic embolization by early surgical intervention for those patients with large vegetations amenable for embolization.

7.1. Empirical Treatment

Treatment of IE should be started promptly after a minimum of three sets of blood cultures. The choice of empirical therapy based upon the guidelines; depends on many factors including; whether the patient had received prior antibiotics, on whether the infection was NVE or PVE, on whether PVE infection is early (<12 months after surgery) or late (>12 months after surgery), and on knowledge of the local epidemiology, including antibiotic resistance and specific blood-culture-negative pathogens. NVE and late PVE regimens should account for the possibility of staphylococci, streptococci, HACEK species and Bartonella species. Treatment must be adjusted immediately after the diagnosis of the pathogen.

7.2. Surgical treatment

Surgery is the treatment of choice in complicated PVE. Sterilization and “cure” by medical treatment alone are rarely possible in active NVE. Surgery was indicated in 41 patients (82%) in our study and was done in 39% and the most common indications for surgery were heart failure in 29 patients (58%), large mobile vegetation in 20 cases (40%), and embolic events in 13 patients (26%), not including pulmonary emboli. Periannular complications in 10 patients (20%) while uncontrolled infection was seen in 4 cases (8%) and recurrence in 2 patients (4%). 37 cases had more than one indication for surgery.

The most frequent indications recorded by Tornos et al. were HF (60%), vegetation size (48%), refractory sepsis (40%), and embolic complications (18%), with a combination of these factors being present in many patients. Surgery was performed in 21 patients (44.7%) in the study by Nashmi et al., they found that the most commonly encountered indications for surgery were large mobile vegetation in 7 (33.3%), heart failure in 4 (19.0%) and severe valvular regurgitation 4 (19.0%); other indications included uncontrolled infection, valvular abscess and systemic embolization.

8. Conclusion

Based upon the results of our prospective study we concluded that: the admission rate of IE in our department is not low, 50
The main limitations to our study were; it was a single center study, the short duration of the study (only one year), the relatively small number of studied cases and the lack of long term follow up of survived IE patients.

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