

Review

Pooled analysis of 1270 infective endocarditis cases in Turkey

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Abstract

Introduction: Despite developments in medicine, infective endocarditis (IE) is still associated with significant morbidity and mortality. In this study it was aimed to systematically review the infective endocarditis literature published or presented from Turkey.

Methodology: To find the published series, one national database (Ulakbim), and three international databases (Scopus, Pubmed and Sci-e) were searched between 31 October-3 November 2014. also, abstracts of congresses by three national congresses were searched for studies regarding infective endocarditis.

Results: Data for 1270 patients (38.3% female, mean age 46.2, 28% prosthetic valve endocarditis) with a diagnosis of infective endocarditis were obtained from 21 reports (18 published articles and three congress abstracts). Of the 18 articles, four were in peer-reviewed medical journals indexed in national databases and 14 were in international databases. There was an underlying heart disease in 51.9% and history of dental procedure was 6.7%. Fever, heart murmur and fatigue were present in 94%, 71.4% and 69% respectively. most commonly involved site was mitral valve (43.3%), followed by aortic (33.8%) and tricuspid valve (6.4%). *Staphylococcus aureus*, coagulase-negative staphylococci and enterococci comprised the 22.8%, 9.7% and 7.5% of the cases while 31.1% were culture-negative. Overall mortality was 23.4%. When we compared series related to years 2008 and before and 2009 and after, the mortality rates were (24.1%-224/931) vs (20.1%-32/159), respectively ($p = 0,31$).

Conclusion: Infective endocarditis is still associated with significant mortality. *S. aureus* seems to be the most common etiologic agent. There was a slight decrease in the recent years in mortality.

Key words: systematic review; review; endocarditis; Turkey; complication; *Brucella*.

J Infect Dev Ctries 2019; 13(2):93-100. doi:10.3855/jidc.10056

(Received 13 December 2017 – Accepted 02 August 2018)

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Introduction

Despite developments in the medicine, antibiotic therapy, surgery and medical care, infectious diseases as well as infective endocarditis (IE) are still associated with significant morbidity and mortality [1-40]. As the life expectancy increases in global scale, the average human gets elder with more cardiac diseases and cardiac operations both of which are important risk factors for infective endocarditis [3]. Infective endocarditis is also an important cause of fever of unknown origin [4,5]. Datasets related to infective endocarditis are usually confined to series with relatively low numbers [6,7]. Epidemiology nosocomial or community-acquired infections change from country to country [8]. Pooled analysis or systematic reviews are beneficial in understanding the epidemiology of rare diseases [9,10]. In this study it was

aimed to review systematically the infective endocarditis literature published or presented from Turkey.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Methodology

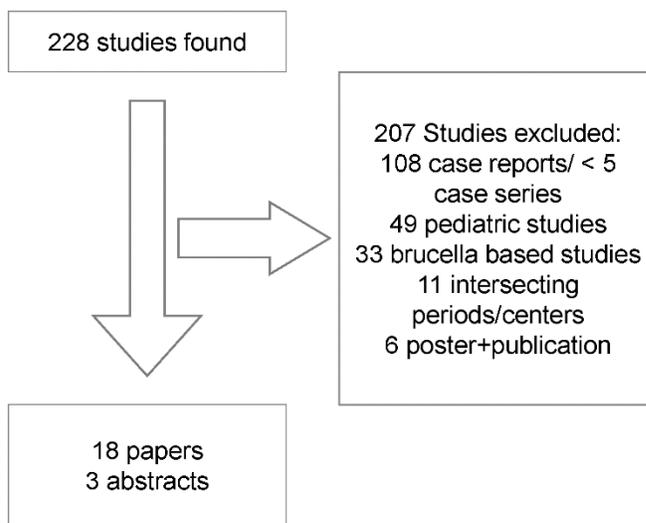
To find the published series, one national database (Ulakbim Turkish Medical Literature Database), and three international databases (Scopus, Pubmed and Science Citation Index-expanded) were searched between 31 October-3 November 2014. Keywords for international databases were “infective endocarditis and address: Turkey” while “(infektif endokardit) or (enfektif endokardit)” were used for national databases. In addition to the published articles extracted by the

above-mentioned methods, abstracts of congresses held by the Infectious Diseases and Clinical Microbiology Society of Turkey (EKMUD), Turkish Clinical Microbiology and Infectious Diseases Association (KLIMIK) and Turkish Antibiotic and Chemotherapy Association (ANKEM) between 2005 and 2014 were searched for studies regarding infective endocarditis. For a more comprehensive review, articles cited in references extracted from sources have also been included.

All abstracts found either in databases or in congress abstract books were analyzed by three separate investigators. For studies that were both published and presented at congresses, only the form of the article was taken into consideration. In case of presentations from a single study with overlapping periods, the study covering the longer duration was chosen. In case of both a single center and multicenter study, the one with higher number was included. The following categories were excluded: (1) articles published before 2005; (2) pediatric series; (3) case reports or series with less than five patients; (4) series related only to *Brucella* endocarditis (these series were excluded because there were too many *Brucella* only series and authors assumed that including these series in the study would affect the results incorrectly).

Data related to gender, age, symptoms and physical examination findings, laboratory findings (white blood cell count, erythrocyte sedimentation rate, C-reactive protein, hemoglobin serum creatinine), underlying heart diseases, risk factors and concomitant diseases,

Figure 1. Flowchart of literature review.



involved infection sites, echocardiographic findings, etiologic agents, complications, mortality and etiology specific mortality were extracted from the included studies (Table 1-8).

Statistical comparisons were made by Chi-square test; a p value less than 0.05 was considered as significant.

Results

Data for 1270 patients (38.3% female, mean age 46,2,) with a diagnosis of infective endocarditis were obtained from 21 reports (Figure 1, 18 published articles and three congress abstracts). Of the 18

Table 1. Symptoms and physical examination findings.

Symptoms and physical examination findings	Percentage of symptom/finding	References
Fever (more than 38 Celsius)	94% (n = 811)	[6,15,19,20,25,29,30,31,33,36,39,40]
Heart murmur	71.4% (n = 269)	[20,30,31]
Fatigue	69.0% (n = 811)	[6,15,20,25,29,31,33,36]
Mental alteration	19.4% (n = 129)	[20,30]
Dyspnea	46.6%(n = 713)	[6,15,20,25,31,33,39]
Focal neurologic symptoms	13.9% (n = 94)	[31,33]
Chilling	35.8% (n = 456)	[15,19,20,31]
Petechiae	19.3% (n = 280)	[6,20,25]
Osler nodes	10.4% (n = 248)	[6,20,36]
Splenomegaly	26.1% (n = 390)	[20,29,30,31,36]
NYHA1/2	44.2% (n = 201)	[6,40]
NYHA3/4	53.5% (n = 449)	[6,15,40]
Atrial fibrillation	12.4% (n = 330)	[15,40]
Laboratory findings		
Mean white blood cell	13.807/mm ³ (n = 629)	[15,20,26,35,37]
]Mean erythrocyte sedimentation rate	66.5 mm/h (n = 468)	[15,20,30,35,38]
C-reactive protein	46.9 mg/dl (n = 528)	[15,26,35,38]
Mean hemoglobin	11.0 (gr/dl) (n = 449)	[15,26,35,37]
Creatinine	1.4 mg/dl (n = 517)	[15,26,35,37]

published articles, four were in peer-reviewed medical journals indexed in national databases and 14 were published in peer-reviewed journals indexed in international databases. Thirteen studies used modified Duke criteria, whereas others used Duke criteria [11,12].

Mean duration of hospitalization and antibiotherapy were 32.8 and 30.2 days, respectively. Underlying disease data were available for 1197 cases and there was an underlying heart disease in 51.9%. Among these, the most common was prosthetic valve (13.6%) followed by rheumatic fever (11%) and pacemaker (5.0%). In 3.4%, there was degenerative heart valve as an underlying heart disease. Other underlying heart diseases are detailed in Table 2.

Risk factors and concomitant diseases data were available for 898 cases. IV drug use history was present in 1% whereas 6.7% had history of dental procedure. Other details of underlying heart diseases and factors for endocarditis are shown in table 2. As concomitant diseases, diabetes mellitus was present in 9.6% whereas 5.2% had chronic renal failure. 5.2% had central catheter and 1.4% had hemodialysis. Other details for risk factors are in Table 3.

When symptoms and physical examination findings were evaluated, fever, heart murmur, fatigue and dyspnea were present in 94%, 71.4%, 69% and 46.6% respectively. Focal neurological symptoms were present in 13.9% and 26.1% had splenomegaly. There was petechiae in 19.3% and 10.5% had Osler nodes. Mental alteration was present in 19.4% and 13.9% had focal neurologic symptoms. 44.3% of the patients classified as NYHA1/2 (New York Heart Association) while 53.5% were classified as NYHA3/4. Other details regarding symptoms and physical examination findings are in Table 1.

Almost 100% had leukocytosis. Mean C-reactive protein level was 46,9 mg/dl. Mean leukocyte count, erythrocyte sedimentation rate and CRP levels were 13807/mm³, 66,5 mm/hour and 46,9 mg/dl respectively. Mean creatinine level was 1,4 mg/dL (Table 1).

Infection site data were available in 1125 cases. The most commonly involved site was mitral valve (43.3%), followed by aortic (33.8%) and tricuspid valve (6.4%). Furthermore, 7.7% of the cases had multivalvular endocarditis (Table 4).

Any vegetation was present in 83.2%. There was endocardial abscess in 15.6%. However, 6.3% had no vegetation on echocardiography. Other echocardiography findings are summarized in Table 5.

Staphylococcus aureus, coagulase-negative staphylococci and enterococci comprised the 22.8%,

9.7% and 7.5% of the cases while 31.1% were culture-negative. Other details of the etiology are summarized in Table 6.

The most common complication was congestive heart failure (38.6%) followed by metastatic infections (35.3%), systemic embolism (23.4%), renal failure (24.6%) and neurological complications (18.7%), cerebrovascular embolism (13.5%), septic shock (12.5%), sinus tachycardia (22.0%), atrial fibrillation (16.6%), paravalvular abscess (13.8%) and chordal rupture (10.9%). Other complications are detailed in Table 7.

Overall mortality was 23.4% (256/1090). To check the effect of time on mortality, we compared series related to years 2008 and before vs 2009 and after, the

Table 2. Underlying heart diseases in percentage (from references number: [6,15,19,20,25-28,29-33,35-37,39,40]).

Disease	% (n)
Bicuspid aortic valve	2.8% (n = 1197)
Degenerative heart valve	3.4% (n = 1197)
Pacemaker endocarditis	5.0% (n = 1197)
Rheumatic fever	11.0% (n = 1197)
Prosthetic valve	13.6% (n = 1197)
Congenital heart disease	2.7% (n = 1197)
Mitral valve prolapsus	1.5% (n = 1197)
Others	11.8% (n = 1197)
Total	51.9% (n = 1197)

Table 3. Risk factors and concomitant diseases in percentage (and numbers) (from references number: [15,19,20,25-27,31,33,36,39]).

Disease	% (n)
DM	9.6% (n = 898)
Hypertension	2.0% (n = 898)
Congestive heart failure	5.5% (n = 898)
IV drug use	1.0% (n = 898)
Recent surgery	5.6% (n = 898)
Dental procedure	6.7% (n = 898)
History of central catheter	5.2% (n = 898)
Haemodialysis	1.4% (n = 898)
Gastrointestinal procedure	1.4% (n = 898)
Chronic renal failure	5.2% (n = 898)

Table 4. Involved infection sites in cases (from references number: [6,15,19,20,25-27,30,31,33-36,39,40]).

Involved site	% (n)
Mitral valve	43.3% (n = 1125)
Aortic valve	33.8% (n = 1125)
Tricuspid valve	6.4% (n = 1125)
Pulmonary valve	0.7% (n = 1125)
Multi valvular	7.7% (n = 1125)

Table 5. Summary of echocardiographic findings in percentage (and numbers).

Pathology	% (n)	References
Prosthetic valve endocarditis	28.7% (n = 1132)	[6,15,19,20,25,26,27,28,29,30,31,33,34,36,38,40]
Vegetation	83.2% (n = 1132)	[6,15,19,20,25,26,27,28,29,30,31,33,34,36,38,40]
Valvular regurgitation	56.5% (n = 918)	[6,15,19,20,25,26,31,34,35,36,38,39]
Aortic regurgitation	15.5% (n = 918)	[6,15,19,20,25,26,31,34,35,36,38,39]
Mitral regurgitation	21.2% (n = 918)	[6,15,19,20,25,26,31,34,35,36,38,39]
Other	20.0% (n = 918)	[6,15,19,20,25,26,31,34,35,36,38,39]
Ejection fraction	53.3% (n = 288)	[15,38]
Abscess	15.6% (n = 544)	[8,20,26,31,33,34,35,36]
No vegetation on echocardiography	6.3% (n = 369)	[15,26]

mortality rates were (24%-224/931) vs (20.1%-32/159), respectively (p = 0,31). 43.9% of the cases received concomitant surgical therapy. When we compared mortality with medical therapy vs medical and surgical therapy, mortality with medical therapy alone was 21.6% (78/360) whereas it was 9.6% (36/374) in cases received both (p = 0,0001). We tried to analyze the difference in mortality vs pathogens but pathogen specific mortality was not detailed in most studies (Table 8). Pathogen specific mortality was highest 28.5% (4/14) in coagulase negative staphylococci whereas it was 27.8% (5/18) in enterococci and 24.5% (12/49) in *S. aureus* (p = 0,88, Table 8).

Discussion

Although many human beings behave as if they will never die, eternal life is not yet possible, and medical practitioners are constantly reminded of this basic truth in their general practice. Infective endocarditis is an emergency of both infectious diseases and cardiology. Urgent diagnosis and treatment are of vital importance [1,2].

Overall mortality of infective endocarditis in this systematic review was 23.5%. When we compared series related to years 2008 and before vs 2009 and after, the mortality rates were (24.1%-224/931) vs

Table 6. Distribution of etiologic agents (%) (derived from references number: [6,12,19,20,25-27,29-39,40]).

Etiologic agent	Total n:1087
Staphylococci	32.5%
<i>Staphylococcus aureus</i>	22.8%
<i>MRSA</i>	4.4%
<i>MSSA</i>	3.8%
<i>Methicillin</i> resistance unmentioned <i>S. aureus</i>	14.5%
Coagulase-negative staphylococci	9.7%
Streptococci	18.1%
Viridans streptococci	13.6%
<i>Streptococcus bovis</i>	0.5%
Other streptococcal species	3.9%
<i>Enterococcus</i> spp.	7.5%
<i>Brucella</i> spp.	4.2%
<i>Micrococcus</i> spp.	0.0%
<i>P. aeuriginosa</i>	0.4%
<i>E.coli</i>	0.4%
HACEK group	0.8%
<i>Candida albicans</i>	0.9%
No growth on culture	31.1%
Positive blood culture	68.8%

Table 7. Endocarditis complications in percentage (and numbers).

Complication	% (n)	References
Congestive heart failure	38.6% (n = 581)	[6,15,31,34]
Neurologic complications	18.7% (n = 107)	[36]
Systemic embolism	23.4% (n = 640)	[6,15,19,31,34,35,36]
Cerebrovascular embolism	13.5% (n = 259)	[26,29,30,36]
Septic shock	12.5% (n = 367)	[15]
Sinus tachycardia	22.0% (n = 86)	[29,31]
AV block	4.1% (n = 72)	[31]
Atrial fibrillation	16.6% (n = 72)	[31]
Paravalvular abscess	13.8% (n = 663)	[6,20,26,31,33,34,35,36,38]
Chordal rupture	10.9% (n = 211)	[6,19]
Renal failure	24.6% (n = 187)	[6]

Table 8. Treatment and mortality in percentage (and number).

Variable	% (n)	References
Duration of hospital stay	32.8 days (n = 391)	[20,26,33,36,37]
Duration of antibiotic treatment (day)	30.2 (n = 507)	[15,19,20,27,33,34,37,38,39]
Number of antibiotics administered	93.7% (n = 447)	[15,19,20,27,32,34,39]
Previous antibiotic use	39.8% (n = 143)	[20,27,30]
Medical treatment	83.8% (n = 656)	[19,20,31,32,34,37,38,39]
Surgical treatment	43.9% (n = 927)	[15,19,20,25,27,28,29,30,31,32,33,34,36,38,40]
Mortality	23.4% (n = 1090)	[15,19,20,25,27,29,30,31,32,33,34,35,39,40]
Mortality with medical therapy only	21.6% (n = 360)	[15,20]
Mortality with surgical treatment	9.6% (n = 374)	[15,20,27]
Mortality in <i>S. aureus</i> endocarditis	24.5% (n = 49)	[20,34]
Mortality in coagulase-negative staphylococci endocarditis	28.5% (n = 14)	[20]
Mortality in viridans streptococci endocarditis	18.5% (n = 27)	[20]
Mortality in enterococcal endocarditis	27.8% (n = 18)	[20]

(20.1%-32/159), respectively ($p = 0.31$). According to World Health Organization statistics from 2013, the mean life expectancy at birth ranged from 49 years in Sierra Leone (as a minimum) to 84 years in Japan (as a maximum). In 1990, the same variable was 38 years in Sierra Leone and 79 years in Japan [3]. The possible causes of increased life expectancy are lifestyle advances in food, sanitation and clean water. Nevertheless, medical advancements such as surgery, chemotherapy, cardiology and transplantation as well as breakthrough developments in infectious diseases, vaccinology and antimicrobial therapy have also played important roles. These developments are also the probable reasons of the decrease in mortality observed in this study. In a systematic review which analyzed global burden of infective endocarditis, the highest case fatality rates were in Southern Latin America followed by Eastern Europe and then East Asia [mean overall risk from all included studies of 0.211 ± 0.104 , and the median was 0.200 (IQR: 0.126)] [13]. In the latest European guideline, mortality rate of European countries was reported to range between 15-30% [14]. As expected, our case fatality rate of 0.235 was within these ranges.

In the presented study it was found that 5.2% and 1.4% of endocarditis cases had history of central catheter and hemodialysis. Central line associated blood stream infection is an important cause of IE especially in cases with chronic renal failure and hemodialysis [2,14,16]. Central line infections are mostly preventable diseases. Proper care during catheterization process and infection control is important tools in the management [16]. In addition, indications to remove the central lines for proper management of Infective Endocarditis should be kept in mind to prevent endocarditis [16].

In European populations, infective endocarditis commonly develops in patients older than 50 years. In a recent Iran (southeastern neighbor of Turkey) study [17] mean age was 56.3 while it was 67 in a Crete-Greek (western neighbor of Turkey) study in our study [18], the mean age of the patients was 46.3. Possible reasons for lower mean age are; more common congenital heart diseases and rheumatic heart diseases. Besides, higher *Brucella* incidence, worse oral hygiene and possible problems in prophylaxis are conceivable [19,20].

Incidence of negative blood culture in our study was 31.1% that is quite higher than American Heart Association's recent studies, which reported rates ranging from 5% to 10% and some other European studies that reported 20% [2,14]. In a study from Crete-Greece this rate was 15.9% and 19% in a recent large Italian series while another recent Iran paper reported that only one of 35 infective endocarditis cases was blood culture positive [17,21]. We may speculate that potential causes for this higher rate of culture-negative infective endocarditis compared to Europe may be performing cultures after antibiotic therapy, low virulence pathogens, lack of appropriate culture or serologic diagnostic systems and poor blood sampling [2,14,22].

Brucella endocarditis is quite common in Southeastern Anatolia [19]. Brucellosis is an endemic disease in Turkey [23,24]. Endocarditis is an important fatal complication of brucellosis [40]. In this study 4.2% of the cases with etiology had *Brucella* endocarditis. Since series related only to *Brucella* endocarditis were not rare that could change the etiologic picture, we excluded the series related only to *Brucella* endocarditis.

Pooled analysis is advantageous in understanding the epidemiology of rare diseases and syndromes. While pooling the data, the inclusion criteria are important. Retrospective studies carry the disadvantage of depending on retrospective hospital records. Although the studies included into this pooled analysis used the Duke criteria and Modified Duke criteria [11,12] for the diagnosis of endocarditis, they all used retrospective clinical data. Another important disadvantage of our study is the heterogeneity of the data. Because of this heterogeneity, the ratios in different variables have different denominators. Although all centers were tertiary-care educational hospitals, possible double report of a single patient from two different centers cannot be excluded. Since abstracts of the congresses held before 2004 could not be reached, they have not been searched and added in the study scope. Although this systematic review includes a large data set, it does not give the exact incidence of the disease. Definitions of all variables included in this paper, were not clear in all studies. In spite of these disadvantages, to our knowledge this is the first pooled analysis on this topic (also in Turkey) gathering the largest data and major clues about the epidemiology and clinical presentation of infective endocarditis in Turkey.

Conclusion

In conclusion, the presented data show that infective endocarditis is still associated with approximately 24% mortality. Infective endocarditis etiology seems to be different from most of the world. Similar with two Mediterranean countries Greece and Italy *S. aureus* seems to be the most important pathogen in infective endocarditis [18,21]. This should be kept in mind in the empirical therapy (excluding penicillinase susceptible penicillins). *Brucella* spp. should also be kept in mind and analyzed properly in possible etiology in endemic regions. The factors that make *S. aureus* the most common pathogen needs to be analyzed. In order to identify the epidemiologic changes, it is necessary to create an appropriate national registration system with fewer bureaucratic entities. Finally more effective infection control measures regarding prevention from infective endocarditis such as better oral and central catheter care as well as proper prophylaxis are urgently needed to further decrease the mortality and morbidity related to it.

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Conflict of interests: No conflict of interests is declared.