THE CASES, TREATMENT AND OUTCOMES OF ENDOCARDITIS PATIENTS AT PHRAMONGKUTKLAO HOSPITAL

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Abstract. Infective endocarditis (IE) is associated with high morbidity and mortality rates. We aimed to determine the causes, treatment and outcomes of IE patients at Phramongkutklao Hospital in order to inform future management decisions. All cases of IE at the study hospital during January 2009-January 2018 were retrospectively reviewed. A total of 79 (5 definite and 28 possible) IE patients were included in the study. Duke's criteria were used to classify definite and possible cases. The median age of study subjects was 59 years; 56% were males. Seventy-seven percent had a positive blood culture. Of the 61 patients with a positive blood culture, 16 had viridans group streptococci, 12 had *Staphylococcus aureus* (4 methicillin-resistant), 7 had *Enterococcus* spp, 7 had coagulase-negative staphylococci, 1 each had *Actinobacillus actinomycetemcomitans* and *Salmonella* Choleraesuis. Twenty-three subjects (29%) died. Among subjects started on empiric treatment where the etiologic organism was resistant to the initial empiric antibiotic, the mortality rate was 50% and among subjects where the organism was sensitive to the initial empiric antibiotic treatment, the mortality rate was 25%. In this study, gram-positive cocci were the predominant cases of IE and the mortality rate was higher when the etiological organism was resistant to the initial empiric antibiotic. Initial empiric antibiotic treatment of IE cases needs to be based on current, regularly updated sensitivity patterns at the treatment hospital to reduce mortality in IE cases.

Keywords: empirical therapy, native valve, prosthetic valve, mortality

INTRODUCTION

Infective endocarditis (IE), has high morbidity and mortality. Ostergaard *et al* (2018) followed 5,576 patients admitted to a hospital with IE and alive at the time of discharge for 10-year period; the death rates were 63% and 42% in the medically and surgically treatment groups, respectively. The incidence rates for IE in Europe have a range of 3-10/100,000/year (Cahill and Prendergast, 2016; Cresti *et al*, 2017). The incidence of IE among Thai patients during 2013, 2014 and 2015 were 4.5%,

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5% and 6 %, respectively (Nakaranurack and Suwanpimolkul, 2017). The risk factors for IE include mitral valve prolapse, aortic sclerosis, other valvular heart disease and prosthetic valve replacement, hemodialysis, diabetes mellitus, human immunodeficiency virus infection and intravenous drug use (Strom *et al*, 2000).

IE can be caused by a variety of bacteria and fungi. The most common organisms reported to cause IE are *Staphylococcus aureus*, *Streptococcus viridans*, group A, C, and G streptococci, enterococci species, HACEK group organisms (*Haemophilus* spp, *Aggregatibacter* spp, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* spp) (Chambers *et al*, 2013), *Brucella* spp, *Coxiella burnetii*, *Bartonella* spp, *Tropheryma whipplei*, *Mycoplasma* spp, *Legionella* spp and fungi organisms (Sharara *et al*, 2016). Nakaranurack *et al* (2017) retrospectively reviewed the organisms causing IE at King Chulalongkorn Memorial Hospital in Bangkok, Thailand during 2006-2015 and found viridans streptococci was the leading pathogen (46%), followed by group B streptococci (27%). A study at tertiary care hospitals in northeastern Thailand found the causative organisms of IE were zoonotic bacteria *(eg, Coxiella burnetti, Bartonella henselae, Streptococcus suis, Erysipelothrix rhusiopathiae* and *Campylobacter fetus*) (Watt *et al*, 2014). This suggests the etiologies of IE may vary by region.

Dickerman *et al* (2007) reported the incidence of stroke among IE patients to be 5.38 per 1,000 patient-days during the first week of therapy and 2.20 per 1,000 patient-days during the second week of therapy. García-Cabrera *et al* (2013) reported the frequency of ischemic neurological complications decreased after 1 week of appropriate antimicrobial treatment (10.9% to 2.8%). This suggest appropriate empiric antibiotic treatment is important for IE case outcomes.

In this study, we aimed to determine the cause, treatment and outcomes of IE cases presenting to the study hospital in order to guide future empiric treatment decision in this patient population.

MATERIALS AND METHODS

Data collection

This study was conducted retrospectively among patients admitted to Phramongkutklao Hospital, a 1,200-bed tertiary care hospital in Bangkok, Thailand, between January 2009 and January 2018. Eligible patients were those diagnosed with IE following modified Duke's criteria (Li *et al*, 2000) (ICD10 diagnostic codes: A32.82, A39.51, B33.21, B37.6, I01.1, I09.1, I33.0, I33.9, I38, and I39). This study was approved by the institutional review board of the Royal Thai Army Medical Department and Phramongkutklao Hospital (Issued No. Q006h/61_Exp).

Patient records were reviewed and the following were collected for each patient: age, gender, history of underlying disease, type of echocardiogram conducted [(transthoracic echocardiogram (TTE) or transesophargeal echocardiogram (TEE)], type of valve affected (native or prosthesis), causative organism, empiric therapy regimen and treatment outcomes.

Statistical analysis

The data were evaluated using the R program (R Development Core Team, 2011). The variables were analyzed using descriptive statistics to determine the frequencies of causative organisms, percentages for demographic data, empiric antibiotic regimens and clinical outcome.

RESULTS

Seventy-nine patients were included in this study. Selected characteristics of study subjects are shown in Table 1. The median age of study subjects was 59 [interquartile range (IQR): 46-69] years. Forty-four subjects were men. The most common comorbidities were: hypertension (32%), mitral regurgitation (24%), diabetes mellitus (23%), dyslipidemia (23%) and chronic kidney disease (19%).

Thirty-eight subjects had a TTE, 8 had a TEE and 7 had both. Fifty-five subjects had definite IE and 28 had possible IE using modified Duke's criteria.

Table 1
Characteristic of study subjects.

Characteristic	Number (%)
Gender	
Male	44 (56)
Median (IQR) age in years	59 (46-69)
Underlying diseases	
Hypertension	25 (32)
Mitral regurgitation	19 (24)
Diabetes mellitus	18 (23)
Dyslipidemia	18 (23)
Chronic kidney disease	15 (19)
Hemodialysis	9 (11)
Heart failure	13 (16)
Echocardiogram	
TTE	38 (48)
TEE	8 (10)
TTE plus TEE	7 (9)
Not reported	26 (33)
Diagnosed by modified Duke's criteria	
Definite IE	51 (65)
Possible IE	28 (35)
Types of IE	
Native valve IE	55 (70)
Prosthetic valve IE	24 (30)
Early-onset prosthetic valve IE	15 (19)
Late-onset prosthetic valve IE	8 (10)
Not reported	1 (1)

IQR, interquartile range; TTE, transthoracic echocardiogram; TEE, transesophageal echocardiogram; IE, infective endocarditis.

Causative organisms

Of the 79 IE subjects, 18 (23%) had a negative culture, 59 (75%) had a culture positive for bacteria and 2 (3%) had a culture positive for a fungus. The most common bacteria found on culture in our study were viridans streptococci (20%), *S. aureus* (15%), coagulase-negative staphylococci (9%) and enterococci spp (9%) (Table 2).

Treatment outcomes

The 3 most common empiric antibiotic regimens used to treat our study subjects were: ceftriaxone monotherapy (14%), ceftriaxone combined with gentamicin (9%) and ampicillin, cloxacillin and gentamicin in combination (8%).

The mortality rate among study subjects was 29%. The mortality rate among subjects started on empiric antimicrobial therapy where the causative organism was 50% resistant and the mortality rate among subjects started on empiric antimicrobial therapy where the causative organism was sensitive was 25%.

Table 2
IE causative organisms among study subjects (N=79).

Organisms	*n* (%)	Mortality rate
Negative culture	18 (23)	3 (4)
Staphylococcus aureus	12 (15)	3 (4)
Methicillin-susceptible *S. aureus*	8 (10)	1 (1)
Methicillin-resistant *S. aureus*	4 (5)	2 (3)
Coagulase-negative staphylococci	7 (9)	2 (3)
Streptococci	30 (38)	9 (11)
Viridans group streptococci	16 (20)	4 (5)
Streptococcus bovis	4 (5)	3 (4)
Streptococcus suis	2 (3)	0
Streptococcus granulicatella	1 (1)	0
Streptococcus agalactiae	2 (3)	1 (1)
Streptococcus pasteurianus	1 (1)	0
Streptococcus Gr C	1 (1)	0
Streptococcus spp	3 (4)	1 (1)
Enterococci spp	7 (9)	2 (3)
Enterococcus faecalis	5 (6)	1 (1)
Enterococcus spp	2 (3)	1 (1)
Corynebacterium spp	1 (1)	0
Aggregatibacter actinomycetemcomitans	1 (1)	0
Salmonella Choleraesuis	1 (1)	1 (1)
Fungi	2 (3)	0
Candida albicans	1 (1)	0
Candida glabrata	1 (1)	0

DISCUSSION

In our study, 71% of IE cases were native valve infections. This finding is similar to 2 previous studies from Western countries and Thailand where most of the IE cases were native valve infections which were 66.7% and 81.7%, respectively (Mirabel *et al*, 2015; Nakaranurack and Suwanpinolkul, 2017). The proportion of prosthetic valve endocarditis cases in our study (30%) was also similar to the report of Mirabel *et al* (2015) (33.3%). However, a study from northeastern Thailand (Watt *et al*, 2015) reported prosthetic valve endocarditis cases (9.9%) because this study was conducted in 2010-2012 when prosthetic valves were lesser used.

In our study, cultures were negative for an organism in 23%, slightly higher than another study from Thailand (18%) (Nakaranurack and Suwanpinolkul, 2017).

Ceftriaxone monotherapy and ceftriaxone and gentamicin combined were the most common antimicrobial regimens used for our study subjects -23% of cases, similar to a previous study (Nakaranurack *et al*, 2017) from Thailand where ceftriaxone was used in 28% of cases.

Aggregatibacteria actinomycetemcomitans was the causative agent of IE in 1 of our subjects. Patients with *A. actinomycetemcomitans* endocarditis usually have intermittent fever and weight loss with a mean duration of symptoms of 13 weeks before IE diagnosis was due to *A. actinomycetemcomitans* has been report to large emboli in up to 63% of infected patients (Paturel *et al*, 2004). However, our patient did not develop any emboli, but did have low-grade fever, dyspnea and 4 kg weight loss during the 2 months prior to admission.

The case of *Salmonella* Choleraesuis in our study was treated empirically with ceftriaxone and azithromycin. Sensitivity testing showed the organism was resistant to ceftriaxone, ceftazidime, cefepime, Cotrimoxazole and ciprofloxacin and was only sensitive to piperacillin plus tazobactam, imipenem, meropenem and ertapenem. A possible mechanism for third generation cephalosporin resistance in *S.* Choleraesuis is the *blaCTX-M-14* gene mutation (Sirichote *et al*, 2010). Our patient received imipenem for 19 days and then he died. We found 4 previous cases of *S.* Choleraesuis causing IE from Poland (Kedrowa, 1957), Russia (Lukoshevichute, 1963), Italy (Giannelli and Moroni, 1968), and Germany (Bayer *et al*, 1971). In the regular cases, it was associated with severe complications, such as a valvular ring abscess, hemopurulent gaseous pericarditis and death.

In our study, the overall mortality rate was 29%, higher than a previous study (17.4%) by Nakaranurack and Suwanpimolkul (2017). One reason for our higher mortality rate could be the high propotion of staphylococcal infections in our study, which has been reported to be associated with higher mortality (Selton-Suty *et al*, 2012). Causative organism resistance to empiric antibiotic treatment was another major cause of the high mortality rate in our study, suggesting treating physicians need to be aware of the sensitivity patterns of these causative organisms at our study institution and make appropriate changes in empiric antimicrobial treatment.

Limitations of this study were it was retrospective and some data were lacking.

In conclusion, gram-positive cocci were the main causative organisms of IE in our study. The mortality rate was high and affected by inappropriate empiric antibiotic treatment. Continuous moni-

toring of causative organisms and their sensitivity testing should be conducted at the study institution and the data should be provided to physicians caring for IE patients.

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