Clinical audit on medical treatment of infective endocarditis in Assiut University Children's Hospital

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Received 30 July 2023
Revised 02 September 2023
Accepted 05 September 2023
Published 23 December 2023

Journal of Current Medical Research and Practice
2023, 8:188–194

Background
Despite advances in diagnostic tools and therapy approaches over the last few decades, pediatric infective endocarditis (IE) remains a complicated condition. IE is associated with considerable morbidity and death.

Aim of the work
This research aims to revise the medical treatment of pediatric patients with IE who were admitted to the Cardiology Unit at Assiut University Children Hospital (AUCH) and how much it is adherent to the international guidelines of American Heart Association (AHA), in addition, to evaluate their outcome.

Subjects and methods
This clinical audit was conducted on 30 pediatric patients with IE who were admitted to the Pediatric Cardiology Unit, AUCH, Egypt from March 2020 to February 2021. In all, 76.7% of enrolled cases with IE received vancomycin 40 mg/kg per 24 h IV in 2 or 3 divided doses and 23.3% received Ceftriaxone at a dose of 100 mg/kg per dose IV or IM daily. Then the treatment was modified according to the blood culture sensitivity test for at least 4 weeks and up to 6–8 weeks in some cases. Transthoracic echocardiography (TTE) was performed for all cases at the beginning, and after finishing the treatment protocol. Evaluation for the development of complications among the studied cases was done.

Results
The median age of the studied participants was 7 years, 83.3% were males. According to Modified Duke Criteria, 73.3% had a definite diagnosis of IE, and 26.7% had a possible diagnosis of IE. All studied cases received immediate assessment, and general and systematic examination. The echocardiographic examination which was done revealed that 83.0% of the studied participants have no valvular lesions. After receiving the empirical treatment, all studied patients received antibiotic therapy according to the blood culture and sensitivity test results. A significant decrease in IVSD, LVESD, LVPWD diameters, and thickness, and a significant improvement in left ventricular systolic function (LVEF and LVFS) was observed in IE patients after receiving treatment. Other cardiac diameters show improvement but do not reach a significant level. Also, the vegetation size shows a significant reduction. Regarding the final outcome of the IE patients who were admitted to AUCH, 53.3% achieved recovery while 46.7% deteriorated.

Conclusion
The international guidelines for the management of IE-diseased children were successfully followed by the Cardiac Unit of AUCH, on average, 85.0% (as we used ceftriaxone as an empirical treatment which is not recommended by AHA), and are associated with a high success rate.

Keywords:
Assiut University Children Hospital, clinical audit, infective endocarditis, pediatric cardiology unit

J Curr Med Res Pract 8:188–194
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2357-0121

Introduction

Infective endocarditis (IE) is an infection of the endocardial surface of the heart that may involve one or more heart valves, the mural endocardium, or a septal defect. It includes acute and subacute bacterial endocarditis as well as nonbacterial endocarditis caused by viruses, fungi, and other microbiologic agents [1]. In industrialized nations, the annual incidence has been estimated to be 3–9 cases per 100 000 people, with male predominance [2].

In acute bacterial endocarditis, the infection progresses rapidly usually caused by staphylococcus aureus even in a healthy heart. In subacute bacterial endocarditis, the infection is usually caused by the lodging of streptococcus viridian in a previously damaged heart valve [3]. The overall recovery rate ranges from 80% to

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85%; for S. viridans and enterococci, it is 90% or greater, and for Staphylococcus species, it is around 50%. A very bad outcome is linked to fungal endocarditis [4].

The mainstay of medical therapy continues to be antibiotic therapy, although, throughout time, the microbiological profile of the pathogenic organisms has altered. Historically, the most common bacterial pathogens have been streptococcal species, especially those from the flora of the oral cavity [5]. However, a growing percentage of IE cases are now caused by staphylococcal species, including methicillin-resistant strains [6].

The current study follows the recommended international guidelines of AHA and ESC, and evaluates its outcome among pediatric patients with IE who were admitted to the Cardiology Unit, at Assiut University Children's Hospital.

Patients and methods

A total of 30 children who were diagnosed to have either definite or possible IE (according to Modified Duke Criteria) [7] were enrolled in this study. The study was conducted in the Pediatric Cardiology Unit, AUCH from March 2020 to February 2021. The study adhered to the guidelines of Assiut University's Ethics Committee (IRB No: 17100677). All caregivers of the children included in this study provided informed written consent. Exclusion criteria were children with a firm alternative diagnoses, those with a resolution of symptoms suggesting IE with antibiotic therapy for ≤4 days, or those who do not meet the criteria for possible IE, and those who refused to participate in the study were also excluded.

Vegetation is an infected soft-tissue lesion linked to the endocardium or an intracardiac prosthesis. Vegetation is seen during echocardiography as an oscillating or nonoscillating echogenicity that is typically related to heart valves. Other areas, such the chordae, chamber walls, or intracardiac devices, may be affected by vegetation [8].

Once established, the vegetation develops into a mass of varying sizes made up of phagocytes, white and red blood cells, fibrin, platelets, and bacterial clumps. The strength and magnitude of bacterial-platelet-neutrophil contacts, which frequently have a core with a very high bacterial concentration and are essentially avascular, are crucial mediators of vegetation size and morphology [9].

Eligible children were subjected to the following. The checklist include:

Points of checklist	Yes	No	Notes
History			
1. Is there a prior congenital or rheumatic heart disease?			
2. Is there a preceding dental or intestinal procedure?			
3. Is there a history of intravenous drug use?			
4. Is there a history of central venous catheter?			
5. Is there a prosthetic heart valve?			
Symptoms: ask about			
1. Fever			
2. Chills			
3. Chest and abdominal pain			
4. Arthralgia			
5. Dyspnea			
6. Night sweat and weight loss			
7. CNS manifestations (stroke, seizures, and headache)			
Signs: ask about			
1. Elevated temperature			
2. Tachycardia			
3. Embolic phenomena (Roth spots, splinter nail bed hge, Osler's nodes)			
4. Janeway's lesions			
5. New or changing murmur			
6. Splenomegaly			
7. Metastatic infection (arthritis, meningitis, pericarditis)			
Investigations			
1. Positive blood culture			1 or 2 samples and causative organism
2. Elevated ESR and CRP			
3. CBC			
4. Urine analysis (hematuria)			
5. Chest radiograph (bilateral infiltrates, pleural effusions, nodules)			
6. Echocardiogram (valve vegetations, prosthetic valve dysfunction, myocardial abscess)			By TTE or TEE

All studied participants received antibiotic therapy according to the blood culture and sensitivity test results following the recommended antibiotic treatments for pediatric IE from the American Heart Association (AHA) [10].

Follow-up

TTE was done at baseline and after finishing the received antimicrobial protocol, to assess the size of vegetation and its effect on the heart structure and function.

Statistical analysis

Data were gathered, edited, coded, and entered into the IBM SPSS (Statistical Package for the Social Sciences, version 20). The qualitative data were presented as numbers (percentage), while

quantitative data were presented as mean ± standard deviation (SD) and ranges. The comparison between categorical data was done by using the Chi-square test or Fisher's exact test when the expected frequency in any cell was less than 5. Student's *t* test was used for comparing quantitative data. The *P* value is defined to be significant at 0.05.

Results

The median age of the studied participants was 7 years (range, 6 months to 16 years), with a male-to-female ratio of 5:1. According to Modified Duke Criteria; 73.3% had a definite diagnosis of IE, and 26.7% had a possible diagnosis of IE (Table 1).

All studied participants received detailed history taking and a general and systematic examination. In addition, the laboratory data namely (complete blood count (CBC), and inflammatory markers) was also done for all studied cases. Six cases (20.0%) suffered from microcytic hypochromic anemia, 24 cases (80.0%) suffered from normocytic normochromic anemia; erythrocyte sedimentation rate and C-reactive protein were raised in 83.3%, and 86.7%, respectively (Table 2).

Echocardiographic examination was done for all enrolled cases and a positive finding, in the form of valvular damage, was documented in five cases (17.0%); two cases (7.0%) had mild, another two cases (7.0%) had moderate, and one case (3.0%) had severe valvular damage. Seventeen cases (56.7%) had intracardiac masses in the form of vegetation at the tricuspid valve in four cases (13.3%), vegetation at the mitral valve in three cases (10.0%), vegetation at VSD in one case (3.3%), another case (3.3%) had vegetation at the left atrium, three cases (10.0) had mass at mitral valve, another three cases (10.0) had mass at the right atrium, two cases (6.7) had mass at the aortic valve, and one case (3.3%) had mass at the pulmonary valve (Table 3).

Regarding the initial empirical therapy until the result of blood culture, 76.7% of enrolled cases received vancomycin at a dose of 40 mg/kg per 24 h IV in 2 or 3 divided doses, and 23.3% received Ceftriaxone at a dose of 100 mg/kg per dose IV or IM daily. Then the treatment was modified according to the blood culture sensitivity test as follows: Gentamicin, Amoxicillin, Rifampicin, Vancomycin, Oxacillin, and Ceftriaxone were used in (74.2%), (45.5%), (37.9%), (25.8%), (21.2%), and (7.6%) of patients, respectively (Fig. 1). The received treatment was prescribed for at least 4 weeks. The detailed findings of the blood culture are presented in Table 4. Staphylococci and Streptococci were the commonest pathogen isolated from 66.7% of cases.

Table 1 Demographic data of the studied patients

Demographic data	Patients (*n*=30)
Age (years)	
Mean±SD	6.63±5.51
Median (range)	0.5–16
Weight (kg)	
Mean±SD	19.54±12.54
Median (range)	7–32
Height (cm)	
Mean±SD	108.5±43.48
Median (range)	65–160
BMI (kg/m^2)	
Mean±SD	16.12±4.01
Median (range)	12.1–20.1
Sex	
Male	25 (83.3)
Female	5 (16.7)
Type of IE	
Definite	22 (73.3)
Possible	8 (26.7)

BMI, body mass index; IE, infective endocarditis. Quantitative data are presented as mean±SD and range; qualitative data are presented as number (percentage).

Table 2 Laboratory data of the studied patients

Laboratory data	Patients (*n*=30)
Complete blood count	
Not done	0 (0.0)
Done	30 (100.0)
Positive finding	
Microcytic hypochromic anemia	6 (20.0)
Normocytic normochromic	24 80.0)
Inflammatory markers	
ESR	
Not done	0 (0.0)
Done	30 (100.0)
Raised	25 (83.3)
CRP	
Not done	0 (0.0)
Done	30 (100.0)
Raised	26 (86.7)

After receiving the appropriate antibiotics, there was a significant decrease in IVSD, LVESD, and LVPWD diameters and thickness, and a significant improvement in left ventricular systolic function (LVEF and LVFS) after receiving treatment for IE. Other cardiac diameters show improvement but not reaching significance (Table 5).

Also, among the nine cases with vegetation, significant improvement in vegetation size was detected by echocardiography after treatment with the appropriate antibiotic ($P < 0.001$), as was observed that two cases showed a decrease in the vegetation size, in three cases vegetations were disappeared, and were stable in four cases, Table 6.

Regarding the final outcome of IE patients who were admitted to AUCH, 53.3% achieved recovery and were

Table 3 Echocardiography findings among the studied patients

	Patients (*n*=30)
Echocardiographic examination	
Not done	0 (0.0)
Done	30 (100.0)
Positive finding	
Valvular damage	5 (17.0)
Mild	2 (7.0)
Moderate	2 (7.0)
Severe	1 (3.0)
Intracardiac masses	17 (56.7)
Vegetation at VSD	1 (3.3)
Vegetation at the tricuspid valve	4 (13.3)
Vegetation at the mitral valve	3 (10.0)
Mass at the pulmonary artery	1 (3.3)
Mass at the mitral valve	3 10.0)
Mass at aortic valve	2 (6.7)
Mass at the right atrium	3 (10.0)
Vegetation at left atrium	1 (3.3)

Qualitative data are presented as number (percentage).

Table 4 Distribution of the studied group according to initial empirical therapy and blood culture tests

Received antibiotics	Patients (*n*=30)
Empirical therapy, *n* (%)	
Vancomycin	23 (76.7)
Ceftriaxone	7 (23.3)
Blood culture	
Staphylococci	10 (33.3)
Methicillin-susceptible staphylococcus aureus (MSSA)	5 (50.0)
Methicillin-resistant S. aureus (MRSA)	1 (10.0)
Methicillin-susceptible coagulase-negative staphylococci (MSCNS)	3 (30.0)
Methicillin-resistant coagulase-negative staphylococci (MRCNS)	1 (10.0)
Streptococci	10 (33.3)
Penicillin G MICa <0.125 (mg/l)	6 (60.0)
Penicillin G MIC: 0.125–0.5 (mg/l)	2 (20.0)
Penicillin G MIC >0.5 (mg/l)	1 (10.0)
Unknown MIC	1 (10.0)
Enterococcus faecalis	1 (3.3)
HACEKb group	1 (3.3)
Candida albicans	1 (3.3)
Polymicrobia	4 (13.3)
Negative blood cultures/valve or misleading cultures due to previous antibiotic therapy	2 (6.7)
Others	1 (3.3)

Qualitative data are presented as number (percentage).

discharged to their home but still on follow-up whereas 46.7% deteriorated [40.0% developed complications and two cases (6.7%) needed urgent surgery] Fig. 2.

Discussion

Pediatric infective endocarditis remains a complicated condition despite advancements in diagnostic and therapeutic strategies over the past few decades [11].

Table 5 Cardiac dimensions measured by echocardiography before and after treatment of IE

Cardiac dimensions	Before-treatment	After-treatment	*P*
PA (mm)	16.11±5.22	16.2±4.89	0.487
LA (mm)	22.63±7.76	22.27±7.54	0.727
AO (mm)	18.00±5.31	17.56±4.89	0.371
RVAW (mm)	4.26±5.90	4.01±4.56	0.703
RV (mm)	10.89±4.98	10.02±4.16	0.648
IVSD (mm)	6.73±2.92	5.89±2.87	<0.04
LVEDD (mm)	37.96±12.78	37.12±8.46	0.652
LVESD (mm)	22.82±10.48	21.20±8.94	<0.04
LVPWD (mm)	4.97±1.98	3.97±1.15	<0.03
LVEF (%)	72.2±8.21	74.64±7.56	<0.04
LVFS (%)	42.3±6.45	45.06±4.65	<0.03
Mitral E (cm/sec)	115.4±38.17	115.16±35.76	0.639
Mitral A (cm/sec)	74.80±28.29	74.19±27.86	0.475
Mitral E/A (ratio)	1.60±0.30	1.43±0.1	0.337

Ao, aortic root; IVSD, interventricular septum dimension; LA, left atrium; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVFS, left ventricular fractional shortening; LVPWD, left ventricular posterior wall end-diastolic thickness; mitral E/A, ratio between E-wave and A-wave; PA, pulmonary artery; RV, right ventricle; RVAW, right ventricular anterior wall. Quantitative data are presented as mean±SD. Significance defined by $P<0.05$.

Table 6 Size of vegetations before and after treatment as detected by echocardiography

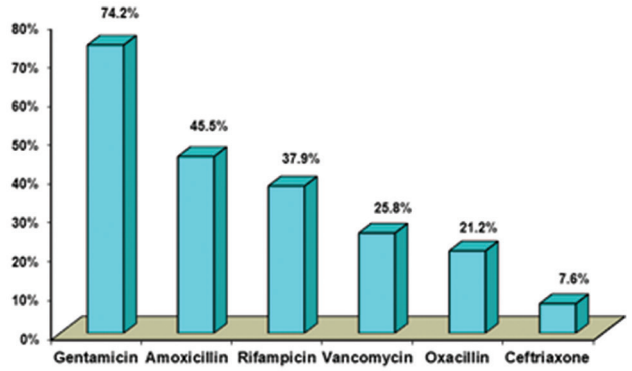
Size of vegetation	*n*=9
Before treatment	
<5 mm	3 (33.3)
5-15 mm	2 (22.2)
>15 mm	4 (44.4)
After treatment	
Decrease in size	2 (22.2)
Gone	3 (33.3)
Stable	4 (44.4)
P	<0.01

Qualitative data are presented as numbers (percentages). Significance defined by $P<0.05$.

According to the underlying conditions, causal pathogens change. In the current study, Staphylococci and Streptococci were the commonest pathogen isolated from the studied participants. In line with the current study, Kim *et al.* reported that Streptococcus species have remained the main IE-causing microbes [12]. Staphylococcus aureus IE has also become more widespread in the developed world, becoming the most common causing bacteria [13]. This finding was previously reported in an Indian study by Ghosh *et al.* [14].

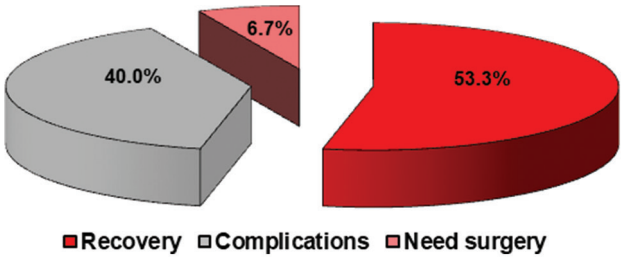
In the present study investigation, Staphylococcus aureus was identified more frequently in individuals with prosthetic valve endocarditis. These bacteria prefer to stick to prosthetic materials. Many other investigations have shown Staphylococcus aureus as the most common cause of prosthetic valve endocarditis [15]. Streptococcus strains, particularly Streptococcus bovis, were described by Barrau *et al.* [16] as the most often

Figure 1



Distribution of the studied cases according to types of antibiotics used after culture and sensitivity test.

Figure 2



Outcome of the studied patients.

occurring pathogen in prosthetic valve endocarditis with Staphylococcus spp. coming in second.

Only 6.7% of the studied cases had negative blood cultures, while Rizk *et al.* [17] observed that a large percentage of their patients had IE that was culture-negative. This could be related to blood cultures being taken and antibiotics being used to treat previous febrile illnesses before hospital admission.

Up till now; the management of IE remains challenging, and mainly based on expert opinion [18, 19]. The present study tried to revise the medical treatment of IE at the Cardiology Unit, AUCH, and how much it is adherent to international guidelines of the American Heart Association (AHA) [10] in addition to evaluating their outcome.

The diagnosis of IE must be made as soon as feasible in order to start the proper empirical antibiotic therapy and to identify patients who are at high risk for problems and may benefit from early surgery. When there is a strong suspicion of IE based on the clinical picture, the patient's risk factor profile, or a history of IE, the diagnosis of IE is frequently made before the results of the blood culture are known. The completion of the diagnostic criteria for IE and the determination of vegetations and incremental valvular insufficiency using echocardiography frequently determine the course of treatment. Although clinical judgment should not be replaced by the use of case definitions to establish an IE diagnosis, the recently modified Duke [7] criteria have proved helpful in both epidemiological and clinical trials as well as in management [20].

While awaiting susceptibility findings, the American Heart Association advised that vancomycin be often used with cefazolin as an empirical treatment for patients with IE caused by S aureus [20]. In the present study, the most commonly used empirical antibiotic was vancomycin at a dose of 40 mg/kg per 24 h IV in 2 or 3 divided doses and 23.3% received Ceftriaxone at a dose of 100 mg/kg per dose IV or IM daily.

However, a review of the literature contrasted the use of empirically combining vancomycin and antistaphylococcal-lactam treatment with vancomycin alone and found that the latter was ineffective against bacteremic MSSA infections, including IE [21].

While the European Society of Cardiology (ESC) advised vancomycin to be supplied initially as an empirical antibiotic therapy for cardiac device-related IE (CDRIE) until microbiological results were known, the ESC additionally recommended using vancomycin for the empirical treatment of MSSA bacteremia/endocarditis [8].

Both the American Heart Association (AHA) and the European Society of Cardiology (ESC) revealed that the optimal empirical treatment is still debated [8, 10]. Initial selection is based on several factors, including suggested regimens for empirical treatment in acute patients. Regimens for native valve endocarditis (NVE) and late prosthetic valve endocarditis (PVE) should include coverage for enterococci, streptococci, and staphylococci [8].

Regarding the management of IE

The present study successfully follows the recommended AHA protocol. AHA recommended Gentamicin 3–6 $mg \cdot kg^{-1} \cdot d^{-1}$ IV divided every 8 h for pediateric IE cases with native valve or 'late' prosthetic valve (>1 year after surgery) infection [10]. In addition, in 2009 the updates of European recommendations suggested using gentamicin in a single daily dose to treat streptococcal endocarditis [22]. In the current study, 74.2% of the studied patients received Gentamicin which is the most prescribed antibiotic.

It is debatable to what extent systemic antibiotic medications lessen the frequency, persistence, kind, or severity of bacteremia connected to dental procedures. Large, well-designed trials demonstrate

that amoxicillin significantly lowers the frequency and duration of bacteremia and alters the species found after pediatric dental procedures [23]. However, AHA did not report a clear statement on whether this antibiotic's bacterial eradication occurs in the gingival crevice or the bloodstream or whether it lowers the risk for IE [10]. In the current study, 45.5% of the studied cases received Amoxicillin.

One of the most popular antibiotics prescribed is amoxicillin. It could be attributed to amoxicillin's potency against oral anaerobes and Streptococci, which makes it suitable for the treatment of odontogenic infections [24]. In line with the current study, the recent Egyptian study by Aly *et al.* (2021) reported that 29.6% of the studied cases with IE received Amoxicillin, and 53.2% Amoxicillin with clavulanic acid due to Amoxicillin's benefit of maintaining its activity against the Beta-lactamases frequently generated by microorganisms linked to odontogenic illness [25]. Amoxicillin cost may be another explanation for its common prescription, as its price is affordable.

In 37.9% of the enrolled cases received Rifampin. AHA recommends adding Rifampin for prosthetic valve endocarditis [10]. Also, Demonchy *et al.* [26] reported that Rifampin was administered to 38% of patients. The only established use for Rifampin is valvular prosthesis staphylococcal endocarditis [27]. Rifampin was being used excessively to treat staphylococcal native valve endocarditis, according to other investigators [28].

The American Heart Association (AHA) advised vancomycin for a wide range of causative pathogens, such as native valve or 'late' prosthetic valve infection (>1 year after surgery), nosocomial endocarditis associated with vascular cannulae, or 'early' prosthetic valve endocarditis (1 year after surgery), and highly susceptible to penicillin G (MBC 0.1 g/ml) and includes most viridans streptococci [10]. However, in the present study vancomycin after being described as an empirical treatment for the majority of the studied cases, after blood culture and sensitivity test results; it was only prescribed for 25.8% of cases. This is not a surprising result, as according to the recent Egyptian meta-analysis of Azzam *et al.* (2023), the author reported that the prevalence of methicillin-sensitive S. aureus (MSSA) among clinical specimens is rising to 63.0%, and it is becoming more susceptible to the antibiotics vancomycin and linezolid, with respective pooled resistance rates of 9% and 5.0% [29].

In 2005, AHA recommended oxacillin for therapy for IE caused by Staphylococci in the absence of prosthetic materials [30]. In 2015, AHA recommended it for Staphylococci (*S aureus* or coagulase-negative staphylococci) infection [10]. In the current study, Oxacillin was received by 21.2%.

Also in 2015, the European Society of Cardiology (ESC) guidelines recommended that most patients with isolated tricuspid IE can benefit from a 2-week course of oxacillin (or cloxacillin) treatment without gentamicin [8].

Ceftriaxone was recommended by AHA to be a highly susceptible strain to penicillin G (MBC ≤0.1 μg/ml) and includes most viridans streptococci, groups A, B, C, G nonenterococcal, group D streptococci (*S bovis*, *S equinus*) at a dose of 100 $mg \cdot kg^{-1} \cdot d^{-1}$ IV divided every 12 h or 80 $mg \cdot kg^{-1} \cdot d^{-1}$ IV every 24 h up to 4 g daily [10]. In the present study, Ceftriaxone was recommended for 7.6% of the studied cases.

Al-Omari *et al.* [31] reported a safe and effective treatment without an increased risk of reinfection and with less medication toxicity after receiving oral ciprofloxacin and rifampicin.

Regarding the final outcome of the IE-studied patients who were admitted to AUCH, we observed significant improvement in cardiac parameters from before to after treatment. Thus, 53.3% achieved recovery, 40.0% developed complications, and 6.7% needed surgery. This came in agreement with Rizk *et al.* [17] who reported that the overall complication rate was 39.4%.

Conclusion

The management of children with IE at the Cardiac Unit of AUCH was successfully following the International Guidelines of the American Heart Association (AHA), on average, 85.0% (as we used ceftriaxone as an empirical treatment which is not recommended by AHA), and was associated with a high success rate. Thus, we recommended revising the empirical treatment for IE that has been recommended at our institution for more practicable, effective, and safe drugs to ensure more favorable outcomes.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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