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Original Article

A Decennium of Etiology and Antimicrobial Susceptibility Patterns in Patients with Infective Endocarditis at a University Hospital, Thailand

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SUMMARY: Infective endocarditis is an infection with a high mortality rate. Antimicrobial therapy is important for treatment, but data on antimicrobial susceptibilities are limited. This retrospective study analyzed data on the causative microorganisms and antimicrobial susceptibility patterns in patients with infective endocarditis 18 years of age or older who received inpatient care between 2006 and 2015 at King Chulalongkorn Memorial Hospital. A total of 213 patients fulfilled the inclusion criteria. *Streptococcus* spp. (54.5%) was the most common organism. Viridans streptococcus (46%) was the leading pathogen, followed by Group B streptococcus (27%). The majority of *Streptococcus* spp. were susceptible to penicillin (82.7%). Among *Streptococcus* spp., *Streptococcus suis* had the highest MIC_{90} of penicillin and cefotaxime (1.65 and 0.95 μg/ml, respectively). There was a statistically significant increase in the MICs of penicillin and cefotaxime for *Streptococcus suis* (P = 0.03 and 0.04). Only 45.5% of *Streptococcus suis* and 77.5% of Viridans streptococcus were susceptible to penicillin. All *Enterococcus* spp. and *Staphylococcus* spp. were susceptible to vancomycin. In conclusion, the prevalence of Group B streptococcus isolates increased among patients with infective endocarditis in Thailand. *Streptococcus suis* had the highest MIC_{90} and proportion of isolates not susceptible to penicillin. Rigorous restriction of the use of antimicrobial agents in animal feeds should be a primary concern.

INTRODUCTION

Despite its rare occurrence in Thailand (1-3), infective endocarditis (IE) is an important disease, as it is a systemic infection associated with a high mortality rate (3-5). In Thailand, the mortality rate ranges from 11% to 25% (1, 3). The identification of the causative microorganisms and data regarding antimicrobial susceptibilities are helpful for empirical therapy in patients with IE. The most common pathogens in IE are Gram-positive bacteria, including *Streptococcus* spp., *Staphylococcus* spp., and *Enterococcus* spp. (3-5); however, there are limited data on the current antimicrobial susceptibility patterns of the microorganisms in patients with IE. This retrospective study analyzed data on the causative microorganisms and antimicrobial susceptibility patterns over a period of 10 years (2006 - 2015) in patients with IE at King Chulalongkorn Memorial Hospital.

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MATERIALS AND METHODS

Patients and population: A retrospective study was conducted at King Chulalongkorn Memorial Hospital, a 1,479 bed, tertiary referral and teaching hospital for the Faculty of Medicine, Chulalongkorn University, and the Thai Red Cross College of Nursing. The inclusion criteria were as follows: (i) IE patients aged 18 years or older (ii) who received inpatient care at King Chulalongkorn Memorial Hospital between 2006 and 2015. Patients with IE were identified based on the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD 10) diagnostic codes. Research Affairs of the Faculty of Medicine at Chulalongkorn University reviewed and approved the study (IRB No.613/58).

Data collection: The data retrieved from medical records included baseline demographics, causative microorganisms, and antimicrobial susceptibilities. Modified Duke criteria were used to define possible and definite cases of IE. For bacterial identification, a 5-ml sample was inoculated into an aerobic bottle of blood culture broth (Versatrek Diagnostic Systems, Cleveland, OH, USA) and incubated at 37°C for 7 days. Viridans streptococcus infections were identified by analytical profile index (API) test. The Kirby-Bauer disk diffusion

method was used for antimicrobial susceptibility testing, according to the 2015 Clinical and Laboratory Standards Institute (CLSI) guidelines. Minimal inhibitory concentrations (MICs) were measured by E-test and interpreted in accordance with CLSI 2015 guidelines (6).

Statistical analysis: Data were analyzed using IBM SPSS Statistics for Windows, version 20.0 (SPSS Co., Ltd. Bangkok, Thailand). Means ± standard deviation (SD) and frequencies were used to describe patients' baseline characteristics. For frequencies, the 50th and 90th percentiles were used to describe antimicrobial susceptibilities. Chi-square tests were used for categorical variables. MICs were compared using Wilcoxon Rank sum tests. Variables were considered to be significant at $P < 0.05$.

RESULTS

A total of 213 patients with IE were diagnosed at King Chulalongkorn Memorial Hospital between January 2006 and December 2015. Their mean age was 50.7 ± 17.7 years and 129 (60.6%) were male. A total of 149 patients were categorized as having definite IE according to modified Duke criteria. Most IE episodes occurred in the native valve (81.7%). Thirty nine (18.3%) patients had diabetes mellitus. Ceftriaxone was the predominant empiric therapeutic regimen (28.2%). Penicillin G plus aminoglycosides regimen (64.4%) and cloxacillin (40.7%) were the predominant documented therapeutic regimens for *Streptococcus* spp. and *Staphylococcus* spp., respectively. The overall in-hospital mortality rate was 17.4 %. The in-hospital *Streptococcus* spp. and *Staphylococcus* spp. mortality rates were 24.3% and 40.5%, respectively. Among 212 hemoculture results, the causative microorganisms were identified in 174 (82%) patients. The baseline characteristics are shown in Table 1. The most common causative microorganisms were gram-positive. Of the gram-positive bacterial isolates, *Streptococcus* spp. were ranked first 90 (54.5%), followed by *Staphylococcus* spp. 54 (32.7%) and *Enterococcus* spp.11 (6.7%). Among *Streptococcus* spp., Viridans streptococcus (46%) was the leading causative microorganism, followed by Group B streptococcus (27%). The species distribution among *Streptococcus* spp. is shown in Figure 1. Among Viridans streptococcus, *Streptococcus oralis* (17%) was most frequently isolated. Among *Staphylococcus* spp., the most common pathogens were *Staphylococcus aureus* (75.9%) and methicillin-resistant *Staphylococcus aureus* 6 (14.6%) isolates.

Antimicrobial susceptibilities over 10 years (2006-2015):

Seventy two (82.7%) *Streptococcus* spp. isolates were susceptible to penicillin, and all *Streptococcus* spp. were susceptible to cefotaxime and vancomycin. The MIC_{50} and MIC_{90} of penicillin were 0.094 and 0.25 μg/ml while those for cefotaxime and vancomycin were 0.125 and

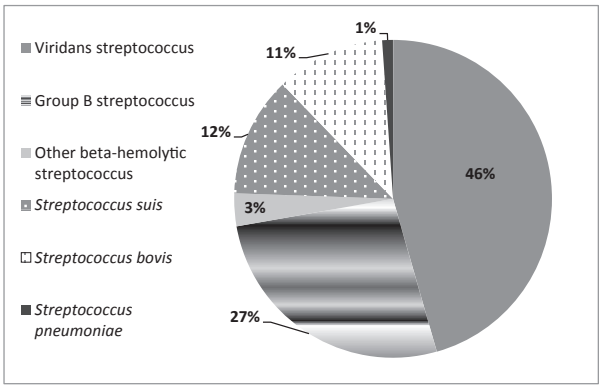

Fig. 1. Species distribution among *Streptococcus* spp.

Table 1. Characteristics of 213 patients with infective endocarditis between January 2006 and December 2015

Characteristic	Value (%)	Characteristic	Value (%)
Male sex	129 (60.6)	*Streptococcus* spp.	90 (54.5)
Age (years); mean±SD	50.7±17.7	-Viridans streptococcus[1)]	41 (46)
Clinical characteristic		*Staphylococcus* spp.	54 (32.7)
Definite case	149 (70)	-*Staphylococcus aureus*	41 (75.9)
Possible case	64 (30)	-Methicillin resistant *Staphylococcus aureus*	6 (14.6)
Valve type		-Coagulase negative *Staphylococcus* spp. (CoNS)	13 (24.1)
Native valve	174 (81.7)	-Methicillin resistant CoNS	6 (46.2)
Prostatic valve	39 (18.3)	*Enterococcus faecalis*	11 (6.7)
Mortality rate	37 (17.4)	Other Gram positive organisms[2)]	10 (6.1)
Streptococcus spp.	9 (24.3)		
Staphylococcus spp.	15 (40.5)		
Microorganisms		Gram negative organisms[3)]	7 (4)
Culture positive	174 (82)	Fungal (*Aspergillus flavus*)	1 (0.6)
Gram positive organisms	165 (94.8)	Zoonosis (*Bartonella henselae*)	1 (0.6)

[1)]: *S.oralis* (7), *S. sanguinis* (6), *S.mitis* (6), *S.constellatus* (3), *S.melleri* (1), *S.intermedius* (1), *S.parasanguinis* (1), *S. angiosus* (1), Other viridians streptococcus (21).

[2)]: *Micrococcus luteus* (1), *Micrococcus* spp. (2), *Gemella morbillorum* (3), *Abiotrophia defective* (1), *Aerococcus* spp. (1), *Granulicatella adiacens* (1), *Gamella haemolysans* (1).

[3)]: *Escherichia coli* (2), *Klebsiella pneumoniae* (1), *Acinetobacter baumannii* (1), *Moraxella* spp. (1), *Burkhoderia cepacia* (1), *Haemophilus influenzae* (1).

Table 2. The antimicrobial susceptibilities of causative microorganisms over 10 years (2006-2015)

Microorganism (total)	Penicillin[b] N (%)					Cefotaxime[c] N (%)			Vancomycin[d,e] N (%)		
	MIC_{50}/ MIC_{90}	Range	S[a]	I[a]	R[a]	MIC_{50}/ MIC_{90}	Range	S[a]	MIC_{50}/ MIC_{90}	Range	S[a]
Streptococcus spp. (87)	0.094/0.25	0.003-2	72 (82.7)	14 (16.1)	1 (1.2)	0.125/0.464	0.016-1	80 (100)	0.5/1	0.19-1	77 (100)
Viridans Streptococcus (40)	0.094/0.25	0.003-0.380	31 (77.5)	8 (20)	1 (2.5)	0.125/0.38	0.016-0.5	37 (100)	0.750/1	0.380-1	35 (100)
Beta-hemolytic Streptococcus (26)	0.064/0.094	0.016-0.125	26 (100)	0 (0)	0 (0)	0.064/0.132	0.032-0.190	22 (100)	0.750/1	0.380-1	21 (100)
Streptococcus suis (11)	0.190/1.65	0.032-2	5 (45.5)	6 (54.5)	0 (0)	0.5/0.95	0.032-1	11 (100)	0.25/0.38	0.19-0.38	11 (100)
Streptococcus bovis (11)	0.094/0.094	0.064-0.094	10 (100)	0 (0)	0 (0)	0.125/0.250	0.094-0.250	11 (100)	0.5/0.725	0.250-0.750	11 (100)
Staphylococcus spp.[f](54)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1.5/2	0.5-2	51 (100)
Enterococcus spp.[g](8)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	2	1.5-3	8 (100)

[a] : Abbreviation: S, susceptible; I, intermediate; R, resistant; NA, not applicable. [b] : CLSI breakpoints: *Streptococcus* spp.: Penicillin, S ≤ 0.12 μg/ml, I 0.25-2 μg/ml, R > 4μg/ml.
[c] : CLSI breakpoints: *Streptococcus* spp.: Cefotaxime, S ≤ 1 μg/ml, I 2 μg/ml, R ≥ 4 μg/ml. [d] : CLSI breakpoints: *Streptococcus* spp.: Vancomycin, S ≤ 1 μg/ml.
[e] : CLSI breakpoints: *Staphylococcus* spp.: Vancomycin, S ≤ 2 μg/ml, I 4-8 μg/ml, R ≥ 16 μg/ml. [f] : MIC_{50} and MIC_{90} of Oxacillin for *Staphylococcus* spp. are 0.75 and 1.9 μg/ml.
[g] : MIC_{50} of ampicillin for *Enterococcus* spp. is 1.5 μg/ml, and all *Enterococcus* spp. are sensitive to ampicillin. The 3 isolates were intrinsically resistance to high levels of aminoglycoside antibiotics (gentamicin 2 isolates and streptomycin 1 isolate).

0.464 μg/ml, and 0.5 and 1 μg/ml, respectively. Among *Streptococcus* spp., *Streptococcus suis* had the highest MIC_{90} of penicillin (1.65 μg/ml) and cefotaxime (0.95 μg/ml), followed by Viridans streptococcus (MIC_{90}: 0.25 and 0.38 μg/ml, respectively). Beta-hemolytic streptococcus and *Streptococcus bovis* had lower MIC_{90} for penicillin (0.094 μg/ml) and cefotaxime (0.132 and 0.25 μg/ml). Only 5 *Streptococcus suis* isolates (45.5%) were susceptible to penicillin.

Thirty one (77.5%) Viridans streptococcus isolates were susceptible to penicillin. All beta-hemolytic streptococcus and *Streptococcus bovis* isolates were susceptible to penicillin. All *Staphylococcus* spp. isolates were susceptible to vancomycin. The MIC_{50} and MIC_{90} of vancomycin were 1.5 and 2 μg/ml, respectively. All *Enterococcus* spp. were susceptible to ampicillin and vancomycin. The 3 *Enterococcus* spp. isolates were intrinsically resistant to high levels of aminoglycoside antibiotics (gentamicin: 2 isolates; streptomycin: one isolate). The antimicrobial susceptibilities of the causative microorganisms over 10 years are presented in Table 2.

Comparison of *Streptococcus* spp., Viridans streptococcus, and *Streptococcus suis* MIC between the first and second 5-year-periods (2006-2010 and 2011-2015):

There was a statistically significant increase in the MICs of penicillin and cefotaxime for *Streptococcus suis* during the second 5-year-period (P = 0.03 and 0.04 for penicillin and cefotaxime, respectively) (Fig. 2A); however, no statistically significant differences in MICs were observed for Viridans streptococcus over the 2 periods (Fig. 2B). The *Streptococcus* spp. MICs of penicillin, cefotaxime, and vancomycin did not differ significantly over the 2 periods (Fig. 2C).

DISCUSSION

The characteristics of IE patients in this study were similar to those of other studies (4,5,7). Most patients were male and most IE episodes occurred in the native valve. When comparing the first and second 5-year-periods (2006-2010 and 2011-2015, respectively), IE patients were significantly older. The proportion of patients with diabetes mellitus increased from 15.6% to 20.8%, but the difference was not statistically significant. The 3 most common causative microorganisms were *Streptococcus* spp., *Staphylococcus* spp., and *Enterococcus* spp., which was similar to the finding of a previous study in Thailand and Japan (1-3,8,9). *Streptococcus* spp. was also reported to be the most causative microorganism in Laos and China (10,11). The causative microorganisms of IE vary according to region. Developed countries have observed an increasing trend in IE caused by *Staphylococcus* spp. (7,12,13). This could be attributed to invasive medical technology, a high population of intravenous drug users, and high *Staphylococcus aureus* nasal carriage rates in Europe and the USA

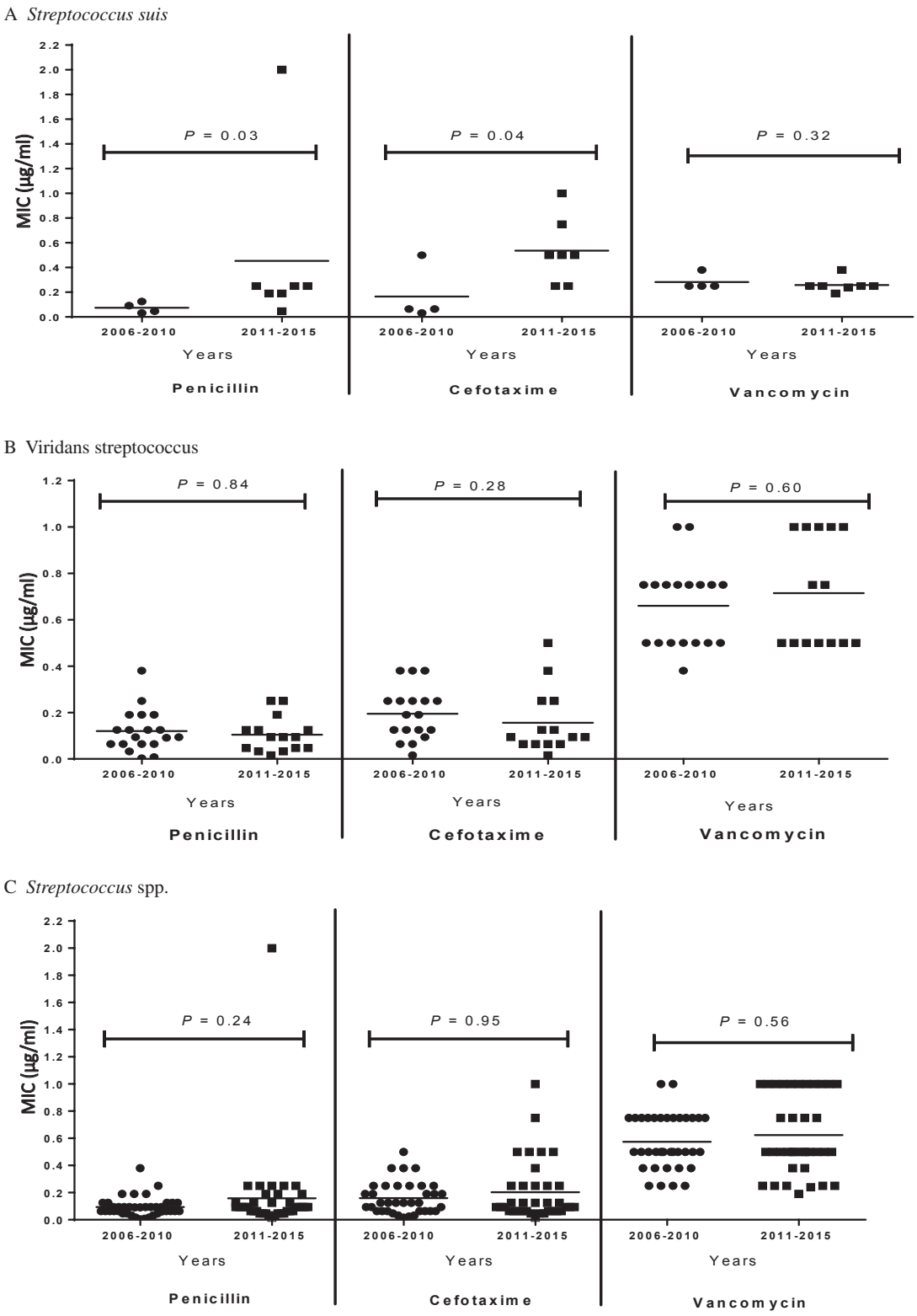

Fig.2. The MICs comparison between the first and second 5-year-periods (2006-2010 and 2011-2015).

compared to Southeast Asia (14). *Staphylococcus* spp. was one of the risk factors for mortality in patients with IE. The overall in-hospital mortality rate in this study was 17.4%, which was lower than that reported in other studies (4,5). This study also showed a higher mortality rate for *Staphylococcus* spp. infections than for Streptococcus spp. infections. Beta-hemolytic streptococcus and *Streptococcus suis* are uncommon causative microorganisms in IE (2,3,15). A study conducted in the USA also showed a decreasing incidence of Group B streptococcus among infants but an increasing incidence of Group B streptococcus in adults. Furthermore, all isolates were susceptible to penicillin, a finding similar to that of the present study (16). There was an increasing

trend in Group B streptococcus infections in Thailand, particularly among patients with bloodstream infections and meningitis (17). Ongoing research is required to explore the reasons for this increasing trend in Group B streptococcus infections. This study also showed an increasing trend in IE caused by Group B streptococcus between the first and second 5-year-periods, from 11.6% to 15.9%, respectively. The reason for this change in the current study may be the increasing age and higher proportion of diabetes mellitus in patients with IE during the second 5-year-period. A previous study from Thailand showed that bacteremia followed by bone and joint infection were the most common clinical manifestations (18). Sixty percent of patients in this study had coinfections, particularly septic arthritis; thus, hematogenous seeding could be the predominant mechanism of infection (19). The incidence of Group B streptococcus IE in this study was higher than that reported in other studies (3,17). Studies in Brazil and Belgium showed only 1.6% and 0.9% of Group B streptococcus IE, respectively (4,20). A meta-analysis showed that the prevalence of *Streptococcus suis* infection is highest in Asia, particularly in Thailand (36%) (21). There were different data for antimicrobial susceptibilities among *Streptococcus* spp., while *Streptococcus suis* had the highest MIC_{90}. One explanation for the increasing *Streptococcus suis* MICs could be the usage of antimicrobial agents in animal feeds, resulting in decreased penicillin susceptibility (62%) in Thailand (22). All *Streptococcus suis* isolates from patients with meningitis in Vietnam were susceptible to penicillin, ceftriaxone, and vancomycin. The MIC_{90} of penicillin and ceftriaxone were 0.047 and 0.125 μg/ml, respectively, which was lower than those in our study (23). The same antimicrobial susceptibility trend in invasive *Streptococcus suis* infection was observed in Poland and Hong Kong (24,25). A retrospective study at Chiang Mai University Hospital, Thailand from 2000 to 2002 showed that all *Streptococcus suis* isolates were susceptible to penicillin (mean MIC_{90} = 0.028 μg/ml), whereas only 45.5% of *Streptococcus suis* in the present study were susceptible to penicillin, with a MIC_{90} of 1.65 μg/ml (26). The present study also showed increased penicillin MIC_{90} in both Viridans and hemolytic streptococci when compared to a previous study (27). Among *Staphylococcus* spp., previous studies reported *Staphylococcus aureus* to be more common than coagulase-negative *Staphylococcus* spp. (2,4,5). The same trend was observed in the current study. The prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in the current study was 14.6%. Most MRSA patients had a prosthetic valve and been admitted to the hospital within 3 months. All *Staphylococcus* spp. were susceptible to vancomycin. *Enterococcus faecalis* was a more common pathogen than *Enterococcus faecium* (4,5). All *Enterococcus* spp. in the present study were *Enterococcus faecalis*, and all were susceptible to ampicillin and vancomycin, a finding similar that of a study conducted in Laos and Turkey (5, 10). According to the 2015 ESC Guidelines for the management of IE, penicillin G is the preferred antimicrobial agent for oral *Streptococcus*, *Streptococcus bovis*, and hemolytic streptococcus. The appropriate dose of penicillin G for *Streptococcus* spp. depends on the MICs. Due to the increasing MIC_{90} but decreasing susceptibility to penicillin in the *Streptococcus suis* and Viridans streptococcus in the present study, a high dose of penicillin G (24 million units/day) or ceftriaxone may be more appropriate empiric therapeutic regimens than low-dose penicillin G (12–18 million units/day) (28). The current study has several limitations. First, the retrospective study design meant that some data were not available. Second, some IE patients were referred from another hospital; thus, some (12%) lacked data on antimicrobial susceptibilities. Third, species identification of Viridans streptococcus during the first period was not available.

In conclusion, *Streptococcus* spp. were the most causative microorganisms in Thailand, and the incidence of Group B streptococcus isolates increased in patients with IE. Elevated MICs and penicillin-non-susceptible isolates were observed among the *Streptococcus suis* and Viridans streptococcus isolates. *Streptococcus suis* had the highest MIC_{90} and greatest proportion of penicillin–non-susceptible isolates; therefore, rigorous restriction of the use of antimicrobial agents in animal feeds should be a primary concern. High-dose penicillin G or ceftriaxone appeared to be more appropriate empiric therapeutic regimens. It is recommended to measure the MICs of penicillin for *Streptococcus* spp. isolates in order to determine the most appropriate antimicrobial regimen.

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Conflict of interest None to declare.

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