

Is Echocardiography Mandatory for All *Streptococcus gallolyticus* Subsp. *pasteurianus* Bacteremia?

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Background: *Streptococcus gallolyticus*, formerly known as one of the *Streptococcus bovis* group, is frequently associated with endocarditis. Current guidelines recommended diagnostic work-up for endocarditis among patients with *S. gallolyticus* bacteremia. However, *S. gallolyticus* subsp. *pasteurianus*, was found to be associated with neonatal sepsis and liver diseases and is less commonly associated with endocarditis compared with *S. gallolyticus* subsp. *gallolyticus*. Our study aimed to identify the risk factors for *S. gallolyticus* subsp. *pasteurianus* endocarditis to help select the patients for echocardiography.

Methods: In this retrospective cohort study, medical records from all adult patients with *S. gallolyticus* subsp. *pasteurianus* isolated from blood cultures at Phramongkutklao Hospital from 2009 to 2015 were reviewed. Patients who had mixed bacteremia or missing records were excluded from the study.

Results: During the study period, *S. gallolyticus* subsp. *pasteurianus* was isolated among 106 individuals. Mean age was 66.9±15.6 years. Most patients (61.3%) were male, with cirrhosis as the most common underlying diseases (46.2%), followed by malignancy and chronic kidney disease. Most common manifestations included primary bacteremia (44.3%), followed by spontaneous bacterial peritonitis (23.6%). Infective endocarditis was found among 9 patients. No patients with cirrhosis or single blood specimen of bacteremia had endocarditis (RR 0; p-value 0.003, and RR 1.35; p-value 0.079). The common complications associated with endocarditis were acute respiratory failure (RR 4.32; p-value 0.05), whereas acute kidney injury was a protective factor (RR 0; p-value 0.01). Among 76 patients who had records of 2-year follow-up, no new diagnosis of endocarditis or malignancy was observed.

Conclusion: Among patients with *S. gallolyticus* subsp. *pasteurianus* bacteremia, echocardiography might not be needed among patients with cirrhosis and without sustained bacteremia.

Keywords: *Streptococcus gallolyticus* subspecies *pasteurianus*, endocarditis, cirrhosis, bacteremia

Background

Formerly, *Streptococcus bovis* was known as a common pathogen for infective endocarditis, usually associated with colorectal neoplasia.^{1,2} However, taxonomy and nomenclature of *S. bovis* were distinguished using a molecular method, such as 16s rRNA gene and *sodA* gene, in six different DNA groups. Common human pathogenic subspecies include *S. gallolyticus* subsp. *gallolyticus* (formerly *S. bovis* biotype I), *S. gallolyticus* subsp. *pasteurianus* (formerly *S. bovis* biotype II/2), *S. infantarius* subsp. *infantarius* and *S. infantarius* subsp. *coli*.²⁻⁶

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Since the introduction of the new taxonomic classification, the disparity of clinical syndromes and patient's underlying diseases between the two subspecies were observed. *S. gallolyticus* subsp. *gallolyticus* bacteremia was strongly associated with endocarditis and colorectal neoplasia.^{7,8} Nevertheless, *S. gallolyticus* subsp. *pasteurianus* was found to be associated with neonatal sepsis, liver diseases and malignancies of the digestive tract, ie, gastric, pancreatic, hepatobiliary and colorectal cancer and is less commonly associated with endocarditis (14–23%) compared with *S. gallolyticus* subsp. *gallolyticus* (50–53%).^{9–15} Nevertheless, many guidelines still recommend diagnostic work-up for endocarditis in all *S. gallolyticus* bacteremia cases, which may result in unnecessary procedures and higher costs of hospitalization.^{16,17}

Because of the lack of large-scale studies investigating the association between *S. gallolyticus* subsp. *pasteurianus* and endocarditis, we aimed to find the risk factors for *S. gallolyticus* subsp. *pasteurianus* endocarditis to help select appropriate patients for echocardiography, expected to minimize the unnecessary investigation.

Objectives

Our primary objective was to determine the risk factors for developing endocarditis among patients with *S. gallolyticus* subsp. *pasteurianus* bacteremia and secondary objective was to determine the 30-day mortality rate of *S. gallolyticus* subsp. *pasteurianus* bacteremia.

Materials and Methods

Study Setting and Design

A retrospective cohort study was conducted. We collected all blood isolates of *S. gallolyticus* subsp. *pasteurianus* obtained from patients from April 2009 to May 2015 at Phramongkutklao Hospital, a 1200 bed teaching hospital of Phramongkutklao College of Medicine, Royal Thai Army, Bangkok, Thailand. The inclusion criteria were participants aged over 18 years with monomicrobial *S. gallolyticus* subsp. *pasteurianus* bacteremia. Participants referred to other hospitals within the first seven days were excluded. Demographic data, patient characteristics, comorbidities, immunosuppressive status, microbiological data and patient outcomes were recorded. The site of infection was defined according to definitions of the Centers for Disease Control and Prevention.¹⁸ Patients whose foci of infection were unidentified were classified as primary bacteremia. Results from echocardiography,

ultrasonography, computed tomography and endoscopic examinations searching for endocarditis, hepatobiliary pathology and colonic lesions were collected. All-cause-30-day crude mortality after the onset of bacteremia was recorded. Participants' medical records were followed up to two years focusing on the finding of new malignancy or endocarditis. The study protocol followed the guidelines of the Declaration of Helsinki and ethics approval was obtained from the Institutional Review Board, Royal Thai army Department.

Microbiological Analysis

Bacterial isolates were collected by the clinical microbiological laboratory at the study hospital. Species were identified using the BACTEC system (Becton Dickson, Sparks, MD). The VITEK 2 automated system (bio-Merieux, Hazelwood, MO) was used to identify bacterial species and subspecies. Antimicrobial susceptibility was determined using the disk diffusion test of various antimicrobial agents including penicillin, gentamicin, clindamycin, ceftriaxone, erythromycin, azithromycin, moxifloxacin, levofloxacin, tigecycline, linezolid, daptomycin and vancomycin. Minimum inhibitory concentrations (MICs) of the isolates to penicillin and ceftriaxone were performed using the E-test. Disk diffusion and MICs were interpreted using the Clinical and Laboratory Standards Institute (CLSI) guidelines.¹⁹

Statistical Analysis

For categorical variables, Fisher's exact test and the Chi-square test were used. The Mann–Whitney test was used to compare continuous variables. For all analyses, a two-sided p-value of 0.05 was considered significant. Potentially significant predictors in the univariate analyses (p-value <0.10) were included in a forward, stepwise multiple logistic regression model to identify the most important factors related to developing endocarditis. All statistical analyses were performed using Stata 12.0 Software (StataCorp, USA).

Results

During the study period, *S. gallolyticus* subsp. *pasteurianus* was isolated in 106 individuals, in whom 191 specimens (88%) blood culture specimens were positive among the overall of 217 specimens taken. The mean age was 66.9±15.6 years. Most patients were male (61.3%), with cirrhosis as the most common underlying disease, followed by diabetes mellitus, malignancy, and chronic

Table 1 Baseline Characteristics of All *S. gallolyticus* Subsp. *pasteurianus* Bacteremic Participants

Characteristic	N	%
Male	65/106	61.3
Age (mean (SD), years)	66.9 (15.7)	
Underlying disease	100/106	94.3
Cirrhosis	49/106	46.2
Diabetes	32/106	30.2
Chronic kidney disease/ESRD	26/106	18.7
Neurovascular disease	11/106	10.4
Hematologic disease	9/106	8.5
Biliary stone	6/106	5.7
Chronic liver disease	4/106	3.8
Autoimmune disease	4/106	3.8
Others	17/106	16
Malignancy diagnosed before presentation	20/106	18.8
Hepatocellular carcinoma	7/20	35
Colorectal cancer	6/20	30
Hematologic malignancy	2/20	10
Others	5/20	25
Clinical syndrome		
Primary bacteremia	47/106	44.3
Spontaneous bacterial peritonitis	25/106	23.6
Endocarditis	9/106	8.5
Intraabdominal infection	4/106	3.8
Biliary tract infection	4/106	3.8
Skin and soft tissue infection	4/106	3.8
CNS infection	4/106	3.8
Other clinical syndromes	9/106	8.5
Complications		
Acute kidney injury	43/106	40.6
Septic shock	40/106	37.7
Respiratory failure	11/106	10.4
Multiorgan failure	9/106	8.5
DIC	7/106	6.6
Number of positive specimens		
≥2 specimens	81/106	76.4
Echocardiography performed	35/106	33
Colonoscopy performed	11/106	10.4
30-day mortality rate	23/106	21.7
Length of hospital stay (median (IQR), days)	12 (6–22)	

kidney disease. Nearly 20% of participants had experienced a malignancy before bacteremic episodes. The most common malignancies included hepatocellular carcinoma, colorectal cancer and hematologic malignancy. The most common clinical manifestations comprised primary bacteremia, followed by spontaneous bacterial peritonitis and endocarditis. Acute kidney injury, septic shock, and

respiratory failure were the three most common complications. Almost all participants had bacteria isolated in two blood culture specimens. The 30-day crude mortality rate was 21.7%, and baseline characteristics of all participants are shown in the [Table 1](#).

Thirty-five patients underwent echocardiography based on clinical presentation and physician decision as [Figure 1](#).

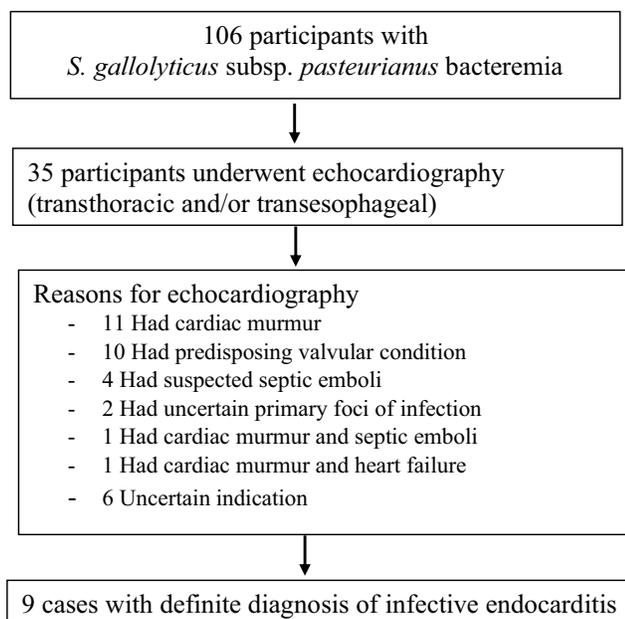


Figure 1 Patients underwent echocardiography.

Nine patients were diagnosed with infective endocarditis as described in Table 2. All of whom had positive blood culture in more than two specimens (RR 1.35; p-value 0.079). None of the cirrhosis patients had endocarditis (RR 0; p-value 0.003). The common complication associated with endocarditis was acute respiratory failure (RR 4.32; p-value 0.05), whereas acute kidney injury served as a protective factor (RR 0; p-value 0.01) as shown in Table 3. Because of the small number of patients with endocarditis, multivariate analysis was not performed.

Among 76 patients with records of two-year follow-up, no new diagnosis of endocarditis or malignancy was observed.

The majority of *S. gallolyticus* subsp. *pasteurianus* was susceptible to antimicrobial agents, with penicillin susceptibility at 97%. However, a high rate of erythromycin resistance (24.5%) was observed as shown in the Table 4.

Discussion

In this cohort study, nearly one half of the patients with *S. gallolyticus* subsp. *pasteurianus* bacteremia presented cirrhosis. This finding was consistent with those of related studies reporting that 15 to 39% of patients had liver diseases or cirrhosis.^{8,14,15}

Regarding the clinical presentations, this study was consistent with others reporting primary bacteremia as the most common clinical presentation, followed by spontaneous bacterial peritonitis, and infective endocarditis.^{8,14,15} About 20% of participants were diagnosed with malignancy before the onset of bacteremia. As in other studies, a correlation between gastrointestinal and other organ malignancies with the bacteremia could not be demonstrated.¹⁴ Although colonoscopy was performed in only 10% of patients, which might have underestimated the true prevalence of precancerous colorectal lesions, no new malignancy was observed after two years among 76 participants.

With the proportion of 8.5%, endocarditis was still an uncommon finding, similar to what had been reported in related studies.^{8,14} None of the endocarditis patients had cirrhosis, which was demonstrated to be a significantly protective factor. The different clinical syndromes between cirrhotic and noncirrhotic patients may be explained by the distinction pathophysiology, host-microbe interaction and bacterial virulence factors. Although, no study to date have compared the adherence potential of *S. gallolyticus* subsp. *pasteurianus* and *S. gallolyticus* subsp. *gallolyticus* to endothelial cells. The surface adhesins such as pili - and

Table 2 Characteristics of Nine Patients with Endocarditis

Case	Age(Yrs.)/Sex	Underlying Disease	Modified Duke's Criteria Major/Minor Criteria	Valve	Treatment	Outcome
1	71/male	Diabetes	2/1	Aortic	Ceftriaxone	Cure
2	43/male	ESRD*Lymphoma	2/1	Mitral	PGS*	Death
3	72/male	Cerebrovascular disease	2/2	Mitral	PGS*	Cure
4	80/male	Hypertension	2/2	Aortic	Ceftriaxone	Cure
5	78/male	Dyslipidemia	2/2	Aortic	Ceftriaxone	Cure
6	44/male	None	2/2	Aortic	PGS*	Death
7	84/male	DiabetesColonic cancer	2/2	Mitral	PGS*	Cure
8	70/female	Hypertension	2/3	Aortic	PGS*	Death
9	51/female	ESRD*	1/3	Aortic	Ceftriaxone	Death

Abbreviations: *PGS, penicillin G sodium; ESRD, End stage renal disease.

Table 3 Univariate Analysis of Factors Associated with Infective Endocarditis in *S. gallolyticus* Subsp. *pasteurianus* Bacteremia

Factor	IE n (%)	Control n (%)	Odds Ratio (95% CI)	p-value
Male	7 (77.78)	58 (59.8)	2.35 (0.46–11.93)	0.477
Age >65 yrs.	6 (66.67)	52 (53.61)	1.73 (0.41–7.32)	0.507
With underlying disease	8 (88.89)	92 (94.85)	0.44 (0.05–4.19)	0.421
Diabetes	2 (22.23)	30 (30.93)	0.64 (0.13–3.26)	0.720
Chronic liver disease	1 (11.12)	3 (3.1)	3.92 (0.36–42.13)	0.300
Cirrhosis	0 (0)	49 (50.52)	0	0.003
Chronic kidney disease	0 (0)	18 (18.56)	0	0.350
End-stage renal disease	2 (22.23)	6 (6.19)	4.33 (0.73–25.58)	0.137
Neurovascular disease	1 (11.12)	10 (10.31)	1.09 (0.12–9.62)	1
Hematologic disease	1 (11.12)	8 (8.25)	1.39 (0.15–12.57)	0.560
Malignancy	1 (11.12)	20 (20.62)	0.48 (0.06–4.08)	0.680
Complication				
Septic shock	1 (11.12)	39 (40.21)	0.19 (0.02–1.55)	0.150
Acute kidney injury	0 (0)	43 (44.33)	0	0.010
Respiratory failure	3 (33.34)	8 (8.25)	5.56 (1.17–26.56)	0.050
Multiorgan failure	2 (22.23)	7 (7.22)	3.67 (0.64–21.13)	0.170
DIC	1 (11.12)	6 (6.19)	1.9 (0.2–17.76)	0.473
Blood culture positive ≥ 2 specimens	8 (88.89)	72 (74.23)	2.78 (0.33–23.33)	0.079

in particular the pilus P11- is absent from the *S. gallolyticus* subsp. *pasteurianus* sequenced strain, and that this pilus plays a major role in infective endocarditis.²⁰ In addition, the adhesin located at the top of the pilus P11 is also able to manipulate the host coagulation system which can further promote endocarditis²¹ accompanied with the expression of blood group antigen sialyl lewis-X (sLex) on human leukocytes increases the adhesion ability of *S. gallolyticus* to endothelial cells.^{22–24} In contrast, the main origin of bacteremia among patients with cirrhosis arise from the fecal microbiome, which might have inferior virulence and less adhesion ability to the endothelium.²⁵

Because *S. gallolyticus* subsp. *pasteurianus*, isolated from two or more different blood cultures, is one of the two major Duke criteria raising the suspicion of endocarditis, echocardiography should be performed.^{16,17} From our findings, because of the lower incidence of endocarditis other than *S. bovis*, this diagnostic procedure might not be needed in patients with cirrhosis, which will decrease the excessive investigation by one half of patients with the bacteremia.

The mortality rate of the bacteremia was higher than related reports.^{8,14} This observation may be explained by

the higher proportion of patients with cirrhosis, which usually had higher complications and mortality rates.²⁵

Although some isolates were intermediate or resistant to beta-lactams using disk diffusion tests, all isolates were susceptible after the MIC measurement when E-test method was performed. This error is due to the poor discrimination ability of disc diffusion tests between penicillin-susceptible and penicillin-intermediate streptococcal populations.^{26,27} As a result, MIC measurement should be primarily used to interpret susceptibility results or to confirm resistance in resistant isolates determined by the disk diffusion method.

Although this is the first study to demonstrate a correlation between *S. gallolyticus* subsp. *pasteurianus* and infective endocarditis among noncirrhotic patients, it had certain limitations. First, although a large number of participants were enrolled in this study, only 8.5% presented endocarditis, which might have overestimated the true association. This small proportion helps confirm that, unlike *S. gallolyticus* subsp. *gallolyticus*, *S. gallolyticus* subsp. *pasteurianus* uncommonly causes endocarditis. Second, the ability of species identification using VITEK 2 system to discriminate between the two subspecies of *S. gallolyticus* is not apparent. Nevertheless, studies comparing between the Vitek 2, conventional biochemistry test

Table 4 Susceptibility Data of 106 Isolates of *S. gallolyticus* Subsp. *pasteurianus*

Antimicrobial Agent	Disk Diffusion Test						Epsilon meter test (E-test)		
	Susceptible		Intermediate		Resistance		MIC Range (ug/mL)	MIC ₅₀ (ug/mL)	MIC ₉₀ (ug/mL)
	No.	%	No.	%	No.	%			
Penicillin	103	97.2	3	2.8	0	0	0.06–0.25	0.09	0.19
Ceftriaxone	97	91.5	2	1.9	7	6.6	0.09–0.75	0.19	0.5
Levofloxacin	89	84.0	6	5.7	11	10.4	N/A	N/A	N/A
Chloramphenicol	101	95.3	2	1.9	3	2.8	N/A	N/A	N/A
Erythromycin	26	24.5	0	0	80	75.5	N/A	N/A	N/A
Vancomycin	106	100.0	0	0	0	0	N/A	N/A	N/A
Linezolid	106	100.0	0	0	0	0	N/A	N/A	N/A

and molecular testing methods (*sodA* sequencing, pyrosequencing of 16S rRNA gene) showed generally acceptable agreement.^{28–30} Finally, due to the retrospective design, factors influencing the physician's reason for the decision to perform colonoscopy and echocardiography was unidentified, which might have underestimated the prevalence of endocarditis and cancer. However, this bias was minimized by the long-term follow-up.

Conclusion

Among patients with *S. gallolyticus* subsp. *pasteurianus* bacteremia, echocardiography might not be needed among patients with cirrhosis and without sustained bacteremia.

Abbreviations

S. bovis, *Streptococcus bovis*; *S. gallolyticus*, *Streptococcus gallolyticus*; *S. gallolyticus* subsp. *gallolyticus*, *S. gallolyticus* subspecies *gallolyticus*; *S. gallolyticus* subsp. *pasteurianus*, *S. gallolyticus* subspecies *pasteurianus*; MIC, minimum inhibitory concentrations; CLSI, Clinical and Laboratory Standards Institute.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

The study protocol followed the guidelines of the Declaration of Helsinki and ethics approval was obtained from the Institutional Review Board, Royal Thai army Department.

The Ethics Committee of the Institutional Review Board, Royal Thai army Department waived the need to obtain consent for the collection, analysis and publication of the retrospectively obtained and anonymized data for this non-interventional study.

Author Contributions

WN prepared proposal, collected the patient data and was a major contributor in writing the manuscript.

VV analyzed and interpreted the patient data regarding to factors related to developing endocarditis in *S. gallolyticus* subsp. *pasteurianus* bacteremia.

J T assisted in patient data collection.

DC supervised the manuscript writing and managed the funding.

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no potential conflict of interest relevant to this article.

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