



## Original Article

## *Staphylococcus lugdunensis* Infective Endocarditis: A Literature Review and Analysis of Risk Factors

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**BACKGROUND/PURPOSE:** Infective endocarditis caused by *Staphylococcus lugdunensis* is a rare disease. Since its first description in 1988, there have only been a few reports of this disease and the causative organism. These publications were primarily case reports and brief case series. We conducted a literature review to identify the nature of the disease and its risk factors.

**METHODS:** We retrospectively reviewed the cases reported between 1988 and 2008 by searching the relevant literature using the keywords “endocarditis” and “*Staphylococcus lugdunensis*” in the Medline database. All cases included met the definition of the modified Duke criteria.

**RESULTS:** For the period 1988–2008, 67 cases from 27 articles were reviewed. The mean age of individuals was 53.9 years. Left-sided valvular endocarditis represented 52 (82.5%) of cases and native-valve endocarditis was evident in 48 (78.7%) of cases. A large proportion (82%) of 50 *S. lugdunensis* strains were susceptible to penicillin. Valve replacement operations were performed in 42 (66.7%) patients and the mortality rate was 38.8%. Univariate analysis showed a higher mortality rate in patients aged more than 50 years, those treated before 1995, those treated with antibiotics alone, and those with growth not detected by echocardiography. Medical treatment alone was the independent risk factor for mortality by multivariate analysis.

**CONCLUSION:** *S. lugdunensis* endocarditis led to substantial morbidity and mortality. Detailed microbiological identification, echocardiography evaluation, and valve replacement may improve the clinical outcome of individuals with *S. lugdunensis* endocarditis.

**KEYWORDS:** infective endocarditis, risk factors, *Staphylococcus lugdunensis*

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### Article History:

Received: Apr 30, 2009

Revised: Jun 20, 2009

Accepted: Aug 25, 2009

## Introduction

*Staphylococcus lugdunensis* is a species of coagulase-negative staphylococci (CoNS), which was first described by Freney et al in 1988. *S. lugdunensis* is differentiated from other CoNS by its ability to produce ornithine decarboxylase and pyrrolidonyl arylamidase (PYR). It is commonly found on the human skin and is a rare contaminant in culture. Since its first identification, many publications have recognized its

pathogenic role in the infections of multiple systems including infective endocarditis (IE), osteomyelitis, septic arthritis, brain abscess, urinary tract infections and soft tissue infections.<sup>1-4</sup>

The first case of IE caused by *S. lugdunensis* was described in 1988.<sup>5</sup> Since then, only a few case reports and brief case series have been published regarding IE caused by *S. lugdunensis*. Most of these reports revealed that IE caused by *S. lugdunensis* could be very aggressive and that mortality was high. These characteristics of *S. lugdunensis* IE differed largely from other CoNS IE.

A 16-year-old girl without remarkable past history was admitted to our hospital because of right flank pain and fever. *S. lugdunensis* was isolated in two separate sets of blood cultures. Echocardiography showed vegetation at the mitral valve, therefore surgery was performed and the outcome was fair without complications.

To provide more insight into the clinical presentations and to evaluate prognostic factors associated with the mortality of this disease, we have extensively reviewed the literature including our one recent case that was treated successfully.

## Methods

We conducted a systematic Medline review covering the period January 1, 1988 through to June 30, 2008. The search terms used were “endocarditis” and “*Staphylococcus lugdunensis*”. The searches focused on peer-reviewed articles published in English. After locating the bibliographic references, we retrieved the abstracts of all selected articles. Two clinicians read the abstracts and complete articles independently and, by consensus, decided upon the articles to be included in the study.

The retrieved articles were included in this study if the case reported met the modified Duke criteria of IE with isolates of *S. lugdunensis*.<sup>6</sup> These articles must contain specific information regarding clinical, microbiological, therapy and outcome variables. For each patient reported, the following variables were recorded: demographic data (age and sex), clinical data (year of diagnosis, portal of entry, sites and types of involved valves and initial echocardiography findings), microbiological data (susceptibility of *S. lugdunensis*), therapy (antimicrobial treatment with or without surgery), and outcome (death or recovery).

## Statistical analysis

Statistics Package for Social Science version 10.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Mean, standard deviation, median and range were calculated for continuous variables. We used  $\chi^2$  test and Fisher's exact test to determine any significant differences between groups with categorical variables. Univariate analyses were conducted to determine the association between potential risk factors and mortality. Variables that were significant in the univariate analysis were included in the multiple factors analysis. A multiple logistic regression model was used to identify those variables independently associated with the risk for mortality. The level of significance for all statistical tests was  $p \leq 0.05$ .

## Results

A total of 67 cases of *S. lugdunensis* IE were included. In our comprehensive review of the literature from 1988 to 2008, 66 cases were identified from 27 articles.<sup>5-7,28</sup> One case was recently treated successfully from our hospital. All of the 67 cases met the modified Duke criteria. None of the patients were injection drug users.

Table 1 shows the overall characteristics of the cases reported. The mean age of cases was 53.9 years (range, 7-82 years). Forty-one (61.2%) cases involved males and 41 cases (61%) were older than 50 years. Forty-five (67.2%) cases were community-acquired with an unknown portal of entry. Thirty-six cases (65.5%) had co-morbidities. Native valve, prosthetic valve and pacemaker IE accounted for 80.6%, 11.9% and 7.5% of cases, respectively. Antimicrobial susceptibility reports were available in 50 patients, of which 82.0% (41 patients) were susceptible to penicillin. About 87% of IE cases occurred on the left side. Of the left-side lesions, mitral valve, aortic valve and both represented 40.3%, 32.8% and 11.9% of the total cases. Eight (11.9%) cases had multi-valvular involvement, and all multi-valvular lesions were on the left side. Eleven (16.4%) cases had the occurrence of embolization. Among 54 patients that received echocardiography examinations, vegetation could be detected in 42 (77.8%) cases. Forty-six (68.7%) cases received both antimicrobial therapy and surgery. The overall mortality rate of *S. lugdunensis* IE was 38.8%.

Table 2 shows the comparison between the dead and surviving cases with *S. lugdunensis* IE. The mortality rates

**Table 1.** Clinical characteristic of 67 cases of *Staphylococcus lugdunensis* infective endocarditis<sup>a</sup>

Characteristics	n (%)
Age (yr)	53.88±19.14 (7–82)
Sex	
Male	41 (61.2)
Female	26 (38.8)
Portal of entry	
Known	22 (32.8)
Unknown	45 (67.2)
Comorbidity	
Yes	36 (65.5)
No	19 (34.5)
Location	
Left-sided	58 (86.6)
Mitral valve	27 (40.3)
Aortic valve	22 (32.8)
Both	8 (11.9)
Right-sided	5 (7.5)
Tricuspid valve	4 (6.0)
Pulmonary valve	1 (1.5)
Pacemaker lead	4 (6.0)
Vegetations on echocardiography	
Yes	42 (77.8)
No	12 (22.2)
Penicillin susceptibility	
Yes	41 (82.0)
No	9 (18.0)
Embolization	
Yes	11 (16.4)
No	56 (83.6)
Surgery	
Yes	46 (68.7)
No	21 (31.3)
Outcome	
Recovered	41 (61.2)
Death	26 (38.8)
Characteristics of valve	
Native valve	54 (80.6)
Prosthetic valve	8 (11.9)
Pacemaker lead	5 (7.5)

<sup>a</sup>Data presented as mean±standard deviation (range) or n (%).

for native valve endocarditis, prosthetic valve endocarditis and pacemaker lead endocarditis were 34.6%, 75% and 20%, respectively. Upon univariate analysis, variables that had significant association with mortality included: age greater than 50 years, medical treatment alone, negative echocardiography findings and diagnosis before 1995. In the multivariate logistic regression analysis, medical treatment alone was an independent risk factor for mortality (odds ratio=4.79; 95% confidence interval=1.16–19.78) (Table 3).

## Discussion

*S. lugdunensis* was first described in 1988 by Freney et al. *S. lugdunensis* is differentiated from other CoNS by the ability to produce ornithine decarboxylase and PYR. *S. lugdunensis* shares some properties with *S. aureus*. Both may express clumping factor and/or a thermostable DNase and have the same virulence determinants.<sup>29</sup> The colony morphology of *S. lugdunensis* also resembles *S. aureus* and may be accidentally identified as *S. aureus*.<sup>30</sup> Approximately 25% of clinical isolates of *S. lugdunensis* produce extracellular slime or glycocalyx, which plays an important role in bacterial colonization and interferes with the phagocytosis-associated activities of neutrophils.

According to the published reports, the clinical presentations of IE caused by CoNS were different from those caused by *S. aureus* in many ways.<sup>31–33</sup> Although *S. lugdunensis* is a CoNS, some reports have showed that the presentation of *S. lugdunensis* IE was more similar to *S. aureus* IE than to IE caused by other CoNS.<sup>34–36</sup>

In our study, *S. lugdunensis* IE usually developed in the cases aged above 50 years. Most patients acquired the infection in the community and the sites of entry were not identified. Most strains of *S. lugdunensis* isolated were sensitive to penicillin. *S. lugdunensis* usually invades the left-side valves with mitral or aortic valve involvement. Sometimes, both mitral and aortic valves could be involved simultaneously. The majority of cases were in the native valve, and IE caused by other CoNS were often hospital-acquired and related to indwelling devices.<sup>31,33</sup> CoNS usually invaded prosthetics valves<sup>37</sup> and most CoNS were resistant to penicillin.<sup>38</sup> These were the characteristics of *S. lugdunensis* that differed from other CoNS.

In our review, 68.7% (46/67) of patients received valve replacement and the rate of surgery was higher than for

**Table 2.** Comparisons between mortal and surviving cases of *Staphylococcus lugdunensis* infective endocarditis

Variables	Total case, <i>n</i>	Mortal case, <i>n</i> (%)	OR (95% CI)	<i>p</i>
Age (yr)				
≤ 50	41	20 (48.7)	1	0.040
> 50	26	6 (23.1)	3.18 (1.06–9.53)	
Sex				
Male	41	18 (43.9)	1	0.320
Female	26	8 (30.9)	1.76 (0.63–4.96)	
Penicillin susceptible				
Yes	41	15 (36.6)	1	0.720
No	9	4 (44.4)	0.72 (0.17–3.11)	
Surgery				
Yes	46	12 (26.1)	1	0.003
No	21	14 (66.6)	5.67 (1.85–17.38)	
Location of vegetations				
Left-sided	57	24 (42.1)		
Right-sided	4	0 (0)		
Pacemaker lead	5	1 (20.0)		
Type of infective valve				
Native valve	52	18 (34.6)		
Prosthetic valve	8	6 (75.0)		
Pacemaker lead	5	1 (20.0)		
Valvular replacement				
Yes				
No				
Source of infections				
Recognized	22	6 (27.3)	1	0.180
Unrecognized	45	20 (44.4)	2.13 (0.71–6.46)	
Vegetations on echocardiography				
Yes	42	10 (23.8)	1	0.040
No	17	12 (70.6)	4.49 (1.16–17.27)	
Diagnosis before 1995				
Yes	21	13 (62.0)	1	0.030
No	42	13 (31.0)	3.63 (1.21–10.86)	

OR=odds ratio; CI=confidence interval.

other pathogens. Four series showed that rates of valve replacement in IE caused by all pathogens ranged from 15% to 45%.<sup>39–42</sup> In a study of 912 consecutive IE cases between 1990 and 2003, significantly more patients with *S. lugdunensis* IE underwent surgery compared with those with *S. aureus* IE (70% vs. 37%); the surgical rate for *S. epidermidis* IE was similar to that for *S. lugdunensis* IE.<sup>2</sup> The mortality rate of *S. lugdunensis* IE was significantly higher than that for *S. epidermidis* IE.<sup>2</sup>

In one series, *S. lugdunensis* IE often caused valve destruction with abscess formation and progressed to congestive heart failure rapidly.<sup>2</sup> The antimicrobial treatment usually could not completely eradicate the infectious processes in most cases. Finally, surgical interventions with valve replacement were often needed in most cases reported. Our study showed that surgery was the only independent risk factor for mortality.

**Table 3.** Multivariate analysis of risk factors for mortality among 67 reported cases of *Staphylococcus lugdunensis* infective endocarditis

Variables	OR (95% CI)	<i>p</i>
Medical treatment alone	4.79 (1.16–19.78)	0.02
Prosthetic valves	4.00 (0.55–29.32)	0.87
Negative echocardiography finding	0.84 (0.27–2.55)	0.33
Age > 50yr	0.37 (0.10–1.42)	0.14
Diagnosis before 1995	0.23 (0.08–1.01)	0.07

OR=odds ratio; CI=confidence interval.

In our review, the mortality rate associated with *S. lugdunensis* IE was 38.8%. In a previous series, the overall mortality of IE ranged from 18.0% to 24.6%.<sup>39–42</sup> In a study of 558 patients with *S. aureus* endocarditis from 2003, the mortality rate was 22.4%.<sup>43</sup> According to Whitener et al in 1993, the mortality rate of CoNS IE was 16%.<sup>33</sup> Compared with these results, the mortality of *S. lugdunensis* endocarditis appeared to be higher. Further analysis should be performed to verify this hypothesis.

Prosthetic valve endocarditis accounted for 11.9% of *S. lugdunensis* endocarditis cases. These patients often had greater comorbidity because of underlying cardiac problems. Deterioration of clinical conditions often delayed operations for valve replacement, and sometimes only conservative treatment was suggested. Overall, pacemaker lead endocarditis constituted 8.2% of *S. lugdunensis* endocarditis cases and the mortality rate was 20%. Removal of the bacteria with antimicrobial therapy was commonly used in these patients and mortality was low compared with other subgroups.

Most isolates of *S. lugdunensis* (82%) were susceptible to penicillin. In studies by Auguera et al and Zinkernagel et al, most isolates of *S. lugdunensis* were susceptible to penicillin.<sup>2</sup> Unlike most CoNS, isolates of *S. lugdunensis* were also generally susceptible to multiple agents. In 2006, Hellbacher analyzed 39 isolates of *S. lugdunensis* and demonstrated that *S. lugdunensis* isolates were generally susceptible to most of the antibiotics currently used.<sup>30</sup> Despite the remarkable susceptibility to a wide array of antimicrobial agents, medical treatment alone was seldom successful and the majority of patients still received surgery for valve replacement.

Most microbiological laboratories do not routinely identify CoNS to the species level. Additionally, both

*S. lugdunensis* and *S. aureus* could be positive in the latex agglutination test because they show similar colony morphology and produce clumping factor. Thus, *S. lugdunensis* might be misidentified as *S. aureus* in routine microbiological laboratory tests. Because of the enhanced virulence and destructive nature of *S. lugdunensis*, the prompt identification of this organism to the species level is essential whenever it is suspected. If a very aggressive form of *S. aureus* IE is encountered, the possibility of *S. lugdunensis* IE should also be considered. There are several biochemical tests able to identify *S. lugdunensis* easily. First, *S. lugdunensis* reveals a negative result in tube coagulase tests. Furthermore, *S. lugdunensis* can be positively differentiated from other CoNS due to positive PYR reaction and positive ornithine decarboxylase activity.

There are some limitations in this study. The main source of information was cases reported in the literature. There is potential for significant selection bias for higher severity, a more complicated course and poorer outcome so that these cases were more likely to be published. In addition, individual investigator's reports could not be standardized for patients' variables and a bias might exist. Some of the sickest patients who might be considered surgical candidates were excluded from surgical options, and certain subgroups of a small number of cases may produce type II errors.

Although uncommon, *S. lugdunensis* is a very aggressive and destructive pathogen with a major role in IE. Examination of the limited data available would suggest surgery appears to be the preferred choice of treatment. In the future, with more cases published from series reports, there should be sufficient cases for more detailed analysis, and hopefully the inherent bias of the analysis will be decreased.

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