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ORIGINAL ARTICLE

Clinical experience and microbiologic characteristics of invasive *Staphylococcus lugdunensis* infection in a tertiary center in northern Taiwan

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Background/Purpose: *Staphylococcus lugdunensis* is a coagulase-negative staphylococcus that cannot be ignored. This study is a comprehensive analysis of the clinical and microbiological characteristics of *S. lugdunensis* bacteremia and sterile site infection during hospitalization.
Methods: This retrospective study included 48 patients with invasive *S. lugdunensis* infection. During the period of March 2002 to July 2012, they had been hospitalized in a tertiary center of northern Taiwan. Demographics, clinical characteristics, and risk factors of mortality were analyzed. All isolates were tested for antimicrobial susceptibility. We identified the staphylococcal cassette chromosome mec (SCCmec) gene for oxacillin nonsusceptible isolates.
Results: The incidence of *S. lugdunensis* in coagulase-negative staphylococci bacteremia was 0.87%. Forty-eight patients were enrolled: *S. lugdunensis* was present in 41 patients with bacteremia, in the ascites of three patients, in the synovial fluid of two patients, in the pleural effusion of one patient, and in the amniotic fluid of one patient. The three most common sources of infection were primary bacteremia (43.8%), catheter-related infection (18.8%), and vascular graft infection (12.5%). All-cause mortality during hospitalization was 20.8% (10/48). All deceased patients were bacteremic. Risk factors associated with in-hospital mortality included a Pittsburgh bacteremia score of 2 or greater, infective endocarditis, and end-

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stage renal disease. Ten (20.8%) isolates were resistant to oxacillin, and 8 isolates were classified as SCCmec type V.
Conclusion: The clinical significance of *S. lugdunensis* should not be ignored, especially in patients with severe comorbidities. An aggressive search for endocarditis is strongly suggested in *S. lugdunensis* bacteremic cases.

Introduction

Staphylococcus lugdunensis, which was named after the city where the organism was initially isolated, is a species of coagulase-negative staphylococci (CoNS). Since its first description in 1988 by Freney et al,[1] this organism has been considered a human pathogen that cannot be ignored.[2] In contrast to other CoNS, the behavior of *S. lugdunensis* is more like that of *Staphylococcus aureus*.[2] *S. lugdunensis* causes a wide spectrum of infections such as skin and soft tissue infection, bone and joint infection, meningitis, catheter-related infection, bacteremia, and infective endocarditis.[2] The most common sites are skin and soft tissue.[3,4] However, most articles have focused on *S. lugdunensis*-related bacteremia and infective endocarditis.[5–7] Some studies on CoNS-related bacteremia have demonstrated that the most common pathogen is *Staphylococcus epidermidis* (incidence rate ranges from 35% to 67.6%), followed by *Staphylococcus haemolyticus* and *Staphylococcus hominis*.[8,9] The mortality rate of patients with CoNS bacteremia ranges from 8% to 14.3%.[8,9] There is no statistical significance in mortality between species. *S. lugdunensis* was not particularly identified in these studies, probably because it constitutes a very small proportion of CoNS.[10] The mortality rate of patients with *S. lugdunensis* bacteremia varies in relation to the presence of infective endocarditis.[11] The mortality rate associated with *S. lugdunensis* endocarditis is reportedly higher than that of *S. aureus* and *S. epidermidis*.[2]

There are limited articles that discuss *S. lugdunensis* in Asia.[4,11–14] In these articles, there are some discrepancies between the infectious origin (i.e., the setting of the acquired infection), involved infectious foci, and antimicrobial susceptibility. In Taiwan, only one study issued the characteristics of community-acquired *S. lugdunensis* infection, whereas a few cases described in other series have focused on infective endocarditis.[5,13,15] Furthermore, only a few studies mention the prevalence and genotypes of oxacillin-resistant *S. lugdunensis*.[4,16,17]

We designed this retrospective study to investigate the clinical characteristics and risk factors of mortality of *S. lugdunensis* bacteremia and sterile site infection. All isolates underwent antimicrobial susceptibility testing. In methicillin-resistant *S. aureus* (MRSA), most health care-associated or nosocomial clones are associated with staphylococcal cassette chromosome mec (SCCmec) type II or type III, and most community-associated MRSA (CA-MRSA) strains are associated with SCCmec type IV.[18] *S. lugdunensis* is short of relevant information. Therefore, we performed SCCmec gene classification for the oxacillin-resistant isolates in our study.

Materials and methods

Setting

This retrospective study was conducted at Chang Gung Memorial Hospital at Linkou (CGMH-Linkou; Taoyuan, Taiwan), a 3715-bed tertiary center in northern Taiwan. It was approved by the research ethics committee (i.e., institutional research board) of CGMH-Linkou (101-4429B).

Study design and patients

Between March 2002 and July 2012, 88 *S. lugdunensis* isolates from sterile sites (e.g., blood, ascites, pleural effusion, synovial fluid, amniotic fluid) were identified through our computer-assisted microbiology laboratory database. Isolates collected from postsurgical drainage tubes were excluded because of the high probability of contamination.

S. lugdunensis isolated from two or more consecutive blood cultures or sterile body fluids of patients were considered clinically significant cases. For patients with a single positive blood culture of *S. lugdunensis*, the clinical significance was determined in accordance with the criteria developed in 1998 by Souvenir et al.[19] Patients were considered to have a clinically significant case if they had one or more of the following: prolonged fever with a temperature of 38°C or greater; hypotension with a systolic blood pressure less than 90 mmHg; leukocytosis or leukopenia with a left-shifted differential; or disseminated intravascular coagulopathy in combination with a major risk factor for potential infection caused by skin flora (including longterm intravascular catheterization used for hospitalized patients, immunosuppressed patients with central lines, patients with peritoneal dialysis or hemodialysis, and other patient populations). Chart review was used to collect data such as demographics, comorbidities, origin of infection, source of infection, illness severity, indications for admission to intensive care units, and outcomes.

Definitions

The Pittsburgh bacteremia score and severe sepsis (defined by surviving sepsis campaign[20]) were used to assess acute illness severity. Acute kidney injury was reflected by an increase in the serum creatinine (SCr) level by at least 0.3 mg/dL (26.5 mmol/L) within 48 hours; as an increase in the SCr level to at least 1.5 times the baseline level, which is known or presumed to have occurred within the previous 7 days; or as a urine volume less than 0.5 mL/kg/h for 6 hours.[21] The origin of infection was defined as: (1)

community-acquired (i.e., infection onset less than 48 hours prior to admission); (2) health care-associated (including a history of hospitalization or surgery in the previous 3 months, residence in a nursing home, chronic dialysis); or (3) hospital-acquired (i.e., infection onset is 48 or more hours after admission). The source of infection was determined by medical records, culture sites, and clinical physician's judgment. The diagnosis of infective endocarditis was based on the modified Duke criteria.[22] Adequate treatment was defined as the use of at least one effective antimicrobial agent, based on susceptibility results within 48 hours of infection onset.

Microbiological tests

The BACTEC 9240 system (Becton, Dickinson and Company, Madison, WI, USA) was used for processing blood cultures, ascites, and synovial fluid. Other sterile body fluids were processed by the conventional method. Isolates were identified as *S. lugdunensis*, according to the following properties: aerobic, Gram-positive cocci in clusters on a Gram's stain; catalase-positive; coagulase-negative; pyrrolidonyl arylamidase test (*PYR* test)-positive; and the presence of ornithine decarboxylase activity.[23] Polymerase chain reaction (PCR)[24] and the *Bruker Biotyper* (database *2.0*) matrix-assisted laser desorption ionization/time of flight mass spectrometry (MALDI-TOF MS) method[25] were used for the second and third reconfirmation tests, respectively. Oxacillin minimal inhibitory concentration (MIC) was performed by using the agar dilution method, based on the Clinical and Laboratory Standards Institute (CLSI) guidelines.[26] The susceptibility data of other antimicrobials (clindamycin, erythromycin, etc.) were tested by the CLSI disc diffusion method.[26] Staphylococcal cassette chromosome mec gene detection was executed by the combination of multiplex PCRs.[27]

Statistical analysis

Categorical variables were compared by using the Fisher's exact test or Chi-square test, as appropriate. Continuous variables were compared by using the Mann-Whitney *U* test. Multivariate analysis was performed by logistic regression with forward LR model to adjust for confounding. All variables with a $p < 0.20$ on univariate analysis were included in the multivariate model. A two-tailed $p < 0.05$ on multivariate analysis was considered statistically significant. All statistical calculations were performed by SPSS version 18.0 software (SPSS Inc., Chicago, IL, USA).

Results

During the study period, 88 *S. lugdunensis* strains were isolated from blood ($n = 81$) or sterile site fluids ($n = 7$). Forty-eight (54.5%) isolates were clinically significant infections. There were 41 patients with bacteremia. The other seven nonbacteremic patients had *S. lugdunensis* isolated from ascites in three patients, synovial fluid in two patients, pleural effusion in one patient, and amniotic fluid in one patient. Table 1 shows the patients' demographics data and clinical characteristics. The three most common comorbidities were hypertension, end-stage renal disease (ESRD), and diabetes mellitus. Nine patients had polymicrobial infections; concomitant non-*S. lugdunensis* isolates were obtained from the blood of seven patients, from the pleural effusion of one patient, and from the amniotic fluid of one patient. Thirty-nine (81.3%) of the 48 patients had fever, and 21 (44.7%) patients had leukocytosis or leukopenia. The Pittsburgh bacteremia scores were two points or more in 12 (29.3%) patients with bacteremia. Fifteen (31%) patients had severe sepsis.

The origin of only five (10.4%) infections could be defined as community-acquired. The proportions of health

Table 1 Demographic characteristics of 48 patients with clinically significant *Staphylococcus lugdunensis* infection

Characteristics	Value
Age (y)	60.238 ± 21.53
Male	23 (47.9)
Comorbid illness	
Hypertension	21 (43.8)
End-stage renal disease	20 (41.7)
Diabetes mellitus	16 (33.3)
Cerebrovascular disease	13 (27.1)
Malignancy	13 (27.1)
Liver cirrhosis	6 (12.5)
Clinical and Laboratory data	
Bacteremia	41 (85.4)
Polymicrobial infection	9 (18.8)
Fever	39 (81.3)
Leukocytosis or leukopenia[a]	21 (44.7)
Anemia[b]	38 (80.9)
Thrombocytopenia[c]	17 (37)
Acute kidney injury[d]	4 (14.8)
Pittsburgh bacteremia score	1.59 ± 3.008
Pittsburgh bacteremia score ≧ 2	12 (29.3)
Severe sepsis	15 (31.3)
ICU required	7 (14.6)
Origin of infection	
Community-acquired	5 (10.4)
Health care-associated	18 (37.5)
Hospital-acquired	25 (52.1)
Source of infection	
Primary bacteremia	21 (43.8)
Catheter-related infection	9 (18.8)
Vascular graft infection	6 (12.5)
Infective endocarditis	4 (8.3)
Bone and joint infection	4 (8.3)
Intra-abdominal infection	2 (4.2)
Skin and soft tissue infection	1 (2.1)
Pelvic infection	1 (2.1)
Adequate treatment	33 (68.8)
Mortality during hospitalization	10 (20.8)

[a] One patient had no leukocyte count data.
[b] One patient had no hemoglobin data.
[c] Two patients had no platelet data.
[d] Twenty patients had end-stage renal disease, and one patient had no creatinine data within 48 hours of infection onset.
Data are presented as *n* (%) or mean ± standard deviation.
ICU = intensive care unit.

Table 2 Comparison of antimicrobial resistance between five community-acquired infections and 43 health care-associated and hospital-acquired infections

	Overall	Community-acquired infection	Health care-associated or hospital-acquired infection	*p*
Clindamycin	9 (18.8)	1 (20)	8 (18.6)	1.000
Erythromycin	12 (25)	2 (40)	10 (23.3)	0.587
Oxacillin	10 (20.8)	0	10 (23.2)	0.569
Penicillin	33 (68.8)	2 (40)	31 (72.1)	0.307
Trimethoprim-sulfamethoxazole	1 (2.1)	1 (20)	0	0.104
Vancomycin	0	0	0	
Teicoplanin	0	0	0	

Data are presented as *n* (%).

Table 3 General data and staphylococcal cassette chromosome mec typing of 10 oxacillin-resistant *Staphylococcus ludgunensis* isolates

Sex, age (y)	Year of isolation	Acquisition	Source of infection	M1 type	M2 type	mecA	SCCmec type
M, 43	2009	Health care- associated	Vascular graft infection	5	C	+	V
M, 71	2009	Hospital-acquired	Primary bacteremia	5	C	+	V
F, 93	2010	Health care- associated	Catheter-related infection	2	A	+	Untypable
M, 63	2010	Health care- associated	Primary bacteremia	5	C	+	V
F, 55	2010	Hospital-acquired	Primary bacteremia	2	A	+	II
F, 47[a]	2010	Hospital-acquired	Catheter-related infection	5	C	+	V
M, 2 mo	2011	Hospital-acquired	Catheter-related infection	5	C	+	V
F, 3 mo	2011	Hospital-acquired	Primary bacteremia	5	C	+	V
M, 81	2011	Hospital-acquired	Primary bacteremia	5	C	+	V
F, 66	2012	Hospital-acquired	Primary bacteremia	5	C	+	V

[a] Isolated from ascites; other strains were isolated from blood.
F = female; M = male; SCCmec = staphylococcal cassette chromosome mec.

care-associated and hospital-acquired infection were 37.5% (*n* = 18) and 52.1% (*n* = 25), respectively. The infectious sources could be identified in 56.3% of patients [catheter-related infection, 18.8% (*n* = 9); vascular graft infection, 12.5% (*n* = 6); infective endocarditis, 8.3% (*n* = 4); bone and joint infection, 8.3% (*n* = 4); intra-abdominal infection, 4.2% (*n* = 2); skin and soft tissue infection, 2.1% (*n* = 1); and pelvic infection, 2.1% (*n* = 1)]. The all-cause mortality during hospitalization was 20.8% (*n* = 10).

All 48 isolates were susceptible to vancomycin and teicoplanin (Table 2). Approximately nine (19%) isolates were

Table 4 Univariate analysis of risk factors for mortality in patients with bacteremia

	Survival (*n* = 31)	Mortality (*n* = 10)	Univariate analysis (*p*)
Age (y)	58.855 ± 24.07	66.86 ± 15.55	0.233
Sex			
Male	16 (51.6)	3 (30)	0.292
Laboratory data			
Polymicrobial bacteremia	7 (22.6)	0	0.164
Leukocytosis or leukopenia	12 (38.7)	4 (40)	1.000
Anemia	23 (76.7)[a]	10 (100)	0.161
Thrombocytopenia	9 (30)[b]	6 (60)	0.135
Acute kidney injury	2 (10)[c]	1 (50)[d]	0.260
Pittsburgh bacteremia score ≧ 2	6 (19.4)	6 (60)	0.040
Comorbid illness			
Hypertension	13 (41.9)	5 (50)	0.724
Diabetes mellitus	10 (32.3)	4 (40)	0.712
End-stage renal disease	11 (35.5)	8 (80)	0.026
Liver cirrhosis	4 (12.9)	1 (10)	1.000
Cerebrovascular disease	8 (25.8)	5 (50)	0.241
Malignancy	9 (29)	1 (10)	0.402

Table 4 (*continued*)

	Survival (n = 31)	Mortality (n = 10)	Univariate analysis (p)
Site of acquisition			
Community-acquired	3 (9.7)	2 (20)	0.580
Health care-associated	10 (32.3)	5 (50)	0.453
Hospital-acquired	18 (58.1)	3 (30)	0.159
Health care-associated or hospital-acquired	28 (90.3)	8 (80)	0.580
Primary site of infection			
Infective endocarditis	1 (3.2)	3 (30)	0.039
Catheter-related infection	5 (16.1)	0 (0)	0.172
Vascular graft infection	5 (16.1)	1 (10)	1.000
Primary bacteremia	15 (48.4)	6 (60)	0.719
Bone and joint infection	2 (6.5)	0	0.566
Skin and soft tissue infection	1 (3.2)	0	1.000
Intra-abdominal infection	2 (6.5)	0	1.000
ICU required	3 (9.7)	3 (30)	0.143
Adequate antibiotics	21 (67.7)	7 (70)	1.000

[a] One patient had no hemoglobin data.
[b] One patient had no platelet data.
[c] Eleven patients had end-stage renal disease.
[d] Eight patients had end-stage renal disease.
Data are presented as n (%) or mean ± standard deviation.
ICU = intensive care unit.

resistant to clindamycin, whereas 12 (25%) isolates were resistant to erythromycin. Ten (20.8%) isolates were resistant to oxacillin and 33 (68.8%) isolates were resistant to penicillin. Only one isolate was not susceptible to trimethoprim/sulfamethoxazole. All 10 oxacillin-resistant strains were health care-associated or hospital-acquired infections. There was no statistically significant difference in antimicrobial susceptibility between isolates from community-acquired infection and health care-associated infection. The oxacillin-resistant strains all carried the mecA gene, and eight (80%) of 10 strains were SCCmec type V. The SCCmec typing in these strains are listed in Table 3.

Tables 4 and 5 summarize the risk factors associated with in-hospital mortality in patients with bacteremia. In univariate analysis, a Pittsburgh bacteremia score of 2 or greater, infective endocarditis, and ESRD were associated with all-cause mortality during hospitalization. A similar result occurred with multivariate analysis.

Discussion

To date, articles on clinically significant *S. lugdunensis* infection report a limited number of cases.[6,11,28] Our study examined the largest number of *S. lugdunensis* infection cases, which were mostly bacteremia cases. Since May 2009, *S. lugdunensis* has routinely been identified in blood specimens in our hospital. Between May 2009 and July 2012, the incidence of *S. lugdunensis* in CoNS bacteremia was 0.87% (67/7673 cases). This was compatible with the findings of a study in Korea that reported an incidence of 0.9%.[11] However, it was much higher than the incidence of 0.3% reported in a study in the United States.[10]

S. lugdunensis is traditionally identified via the biochemical methods mentioned previously, which are time-consuming and can have false interpretations because of artificial mistakes such as mixed cultures, contaminated mineral oil used in the ornithine decarboxylase test, and the interpretation of weak positive findings in ornithine decarboxylase activity test. Polymerase chain reaction offers a faster and more accurate method for identifying bacteria strains, which can facilitate appropriate therapy. In our study, 58 patients were originally believed to have invasive *S. lugdunensis* infections, but PCR identified other CoNS in 10 patients (data not shown). In addition, we used a MALDI-TOF MS method as the third confirmation test for *S. lugdunensis* identification. The result excellently correlated with PCR. Since 2007, the identification of bacteria species by the MALDI-TOF MS method has been reported, and several articles involve *S. lugdunensis* identification.[29,30] These studies demonstrate that MALDI-TOF MS is a reliable and rapid method for identifying staphylococci.

Most patients in our study had health care-acquired or hospital-acquired infections. Community-acquired infection affected only five (10.4%) patients, which was lower than in a previously reported study.[11] In cases of health care-associated and hospital-acquired infections, 19 (44.2%) of 43 patients had ESRD that required hemodialysis or peritoneal dialysis. Because *S. lugdunensis* is a skin commensal,[2] patients undergoing frequent invasive procedures may have a higher risk of infection. The other three most common comorbidities in our patients were hypertension, diabetes mellitus, and cerebrovascular disease. All three comorbidities may cause patients to require frequent hospitalizations or longterm care.

Four (9.8%) of 41 bacteremic patients were diagnosed as having infective endocarditis (IE). One patient had pacemaker-associated IE, which has been rarely reported in previous studies.[2,31] All four patients were native valve IE, and three of these patients had left-sided valve involvement. All IE patients received surgery, and the mortality was relatively high (75%) in our study. A previous article[5] described the

Table 5 Multivariate analysis of risk factors for all-cause mortality in patients with bacteremia

	OR (95% CI)	*p*
Pittsburgh bacteremia score ≧ 2	55.464 (3.096–993.596)	0.006
Infective endocarditis	293.497 (4.939–17439.534)	0.006
End-stage renal disease	27.025 (1.572–464.454)	0.023

CI = confidence interval; OR = odds ratio.

characteristics of S. lugdunensis-related endocarditis, which were of community-acquired origin, predominantly affects left-sided valves, susceptible to penicillin, patients required surgery, and most patients have native-valve involvement. Our IE patients matched most of these characteristics, but had a higher mortality rate (75% vs. 38.8%). Some studies have mentioned possible IE-related virulence proteins such as fibrinogen-binding protein and von Willebrand factor binding protein[2,32,33]; however, these data are fragmentary and scarce. A search for the integration of virulence factors in IE-related strains may be needed.

S. lugdunensis infections, other than bacteremia, were primarily catheter-associated. Three patients had continuous ambulatory peritoneal dialysis tube-associated peritonitis, and one patient had chest tube drainage-related empyema. There were also two cases of septic knee arthritis, which has been rarely reported in previous studies.[2]

There was one case of pelvic infection, which was diagnosed as chorioamnionitis. The patient was a 34-year-old female who was admitted because of high fever. Just 2 weeks prior to admission, she received McDonald's sutures. The specimen was obtained via amniocentesis. The culture was polymicrobial. Other microorganisms included group B *Streptococcus* and *Peptostreptococcus*. The patient underwent an abortion because of unstable hemodynamics. Her condition improved dramatically after the abortion. There are few studies reporting amniotic fluid infection related to *S. lugdunensis*.[34] The role of this organism in chorioamnionitis and septic abortion remains undefined.

The crude mortality of our patients was 20.8% ($n = 10$), and all of these patients had bacteremia. In previous studies, the mortality rate of *S. lugdunensis* bacteremia ranged from 0% to 23%.[6,11,35] A Pittsburgh bacteremia score of 2 or greater, ESRD, and IE were independently associated with mortality in all patients with bacteremia. Severe underlying diseases that may be responsible for mortality in most conditions have been described in a previous study.[11]

The resistant rate of *S. lugdunensis* to oxacillin and penicillin varies widely in published studies.[2–4,6,10,11,36] In most studies,[3,4,6,36] oxacillin resistance was low (at most 5%). Our study showed a higher oxacillin resistance rate (20.8%), which was similar to the rate in the Korean study.[11] In most studies,[3,4,6] the origin of infection was primarily by community acquisition. However, all oxacillin-resistant strains in our study were health care-associated or hospital-acquired infections, which was similar to the finding of the Korean study.[11] Antibiotic use and invasive procedures in noncommunity-acquired infections may explain this situation. Prior to 2005, different breakpoints were used for the oxacillin minimal inhibitory concentration (MIC) of *S. lugdunensis*.[2,37] Since 2005, the CLSI revised the oxacillin breakpoints of *S. lugdunensis* as those established for *S. aureus* (MIC of 2 μg/mL or less, categorized as "susceptible"; MIC of 4 μg/mL or greater, categorized as "resistant").[2,37–39] This may also cause the different result in oxacillin susceptibility.

A few studies report the presence of SCCmec genes in oxacillin-resistant strains of *S. lugdunensis*.[3,4,12,16] However, the number of resistant strains is small (ranging from 1 strain to 3 strains). In our study, all 10 oxacillin-resistant *S. lugdunensis* isolates carried the SCCmecA gene. Eight isolates were classified as SCCmec type V, one isolate was classified as SCCmec type II, and one isolate could not be classified. In Taiwan, SCCmec type V was found primarily in community-acquired *S. aureus*, especially in subtype V_T.[40] The difference between *S. lugdunensis* and *S. aureus* in the SCCmec type V gene may need to be explored.

There are some limitations in this study. *S. lugdunensis* is an uncommon pathogen, and the number of cases may still be insufficient to demonstrate fully the clinical characteristics. There is no accurate definition for the clinical significance of a single blood culture positive for CoNS. This may have added bias in the case collection.

S. lugdunensis accounts for only a small proportion of CoNS bacteremia; however, its clinical significance should not be ignored—especially in patients with severe comorbidities. The clinical spectrum of *S. lugdunensis* infections varies widely. An aggressive search for the possibility of infective endocarditis is strongly indicated among patients with *S. lugdunensis* bacteremia.

Conflicts of interest

All authors declare no conflicts of interest.

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