

Properties of *Staphylococcus lugdunensis* in Children

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Abstract

Background. *Staphylococcus lugdunensis* is one of the clinically important coagulase-negative staphylococci. The purpose of this study was to elucidate the microbiological features of *S. lugdunensis* in hospitalized children. **Methods.** From January 2012 to December 2019, all isolates were retrospectively screened for *S. lugdunensis*. **Results.** Twenty-five children were eligible for study. Nineteen and six children were classified into a critical care unit group (Group A) and a general medical ward group (Group B), respectively. The prevalence of methicillin-resistant *S. lugdunensis* was significantly higher in Group A than in Group B (68.4% vs 0%; $P < .01$). Eleven children (44%) had *S. lugdunensis* infections, while the remaining children were colonized. Six of the 11 infected children (55%) had healthcare-associated infections. Moreover, 3 isolates exhibited the methicillin resistance. **Conclusions.** The bacteriological characteristics of *S. lugdunensis* differ depending on patient background. Selection of antibiotic treatment should in part rely on patient background data.

Keywords

bacteremia, coagulase-negative staphylococcus, sepsis, healthcare-associated infection

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Introduction

Staphylococcus lugdunensis is a coagulase-negative staphylococcus (CoNS) first described by Freney et al.¹ It is typically considered a member of the normal human skin flora. Even though it is a CoNS, it is known to cause quite severe infections, resembling those of *Staphylococcus aureus*.² Recently, studies of adult populations have resulted in the recognition of its pathogenic role in diseases, such as infective endocarditis, osteomyelitis, septic arthritis, brain abscess, urinary tract infections, and soft tissue infections.^{2–6} Therefore, when isolated in culture, *S. lugdunensis* should be considered a true pathogen, rather than a contaminant, especially if isolated in culture from otherwise sterile patient sample material.

Appropriate administration of antimicrobials is important in the treatment of severe bacterial infection. In the treatment of *S. lugdunensis* infections, the choice of antibiotics depends on whether the detected *S. lugdunensis* is methicillin-resistant or not. Several studies involving *S. lugdunensis* have focused on

community-acquired infections. Data on the clinical and microbiological characteristics of *S. lugdunensis* infection in children remain limited, especially infections in hospitalized children. Moreover, limited data is available pertaining to the potential influence of ward characteristics (eg, pediatric intensive care unit [PICU]; neonatal intensive care unit [NICU]; growing care unit [GCU]; pediatric high-care unit [PHCU]; and general medical ward) on the clinical and microbiological characteristics of *S. lugdunensis*, especially not in children.³

The aim of this study was to elucidate the clinical and microbiological features of *S. lugdunensis* isolated from children admitted to the hospital.

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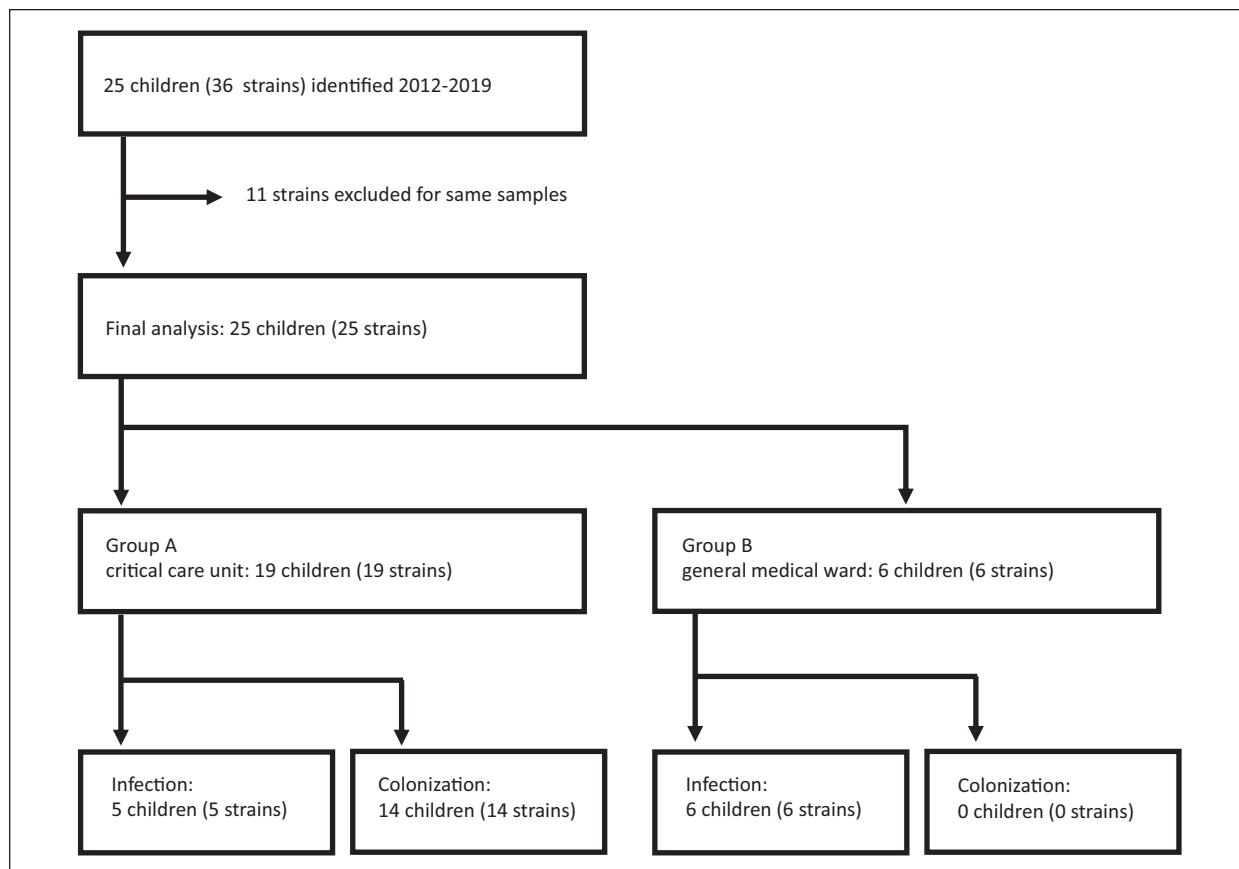


Figure 1. Flow diagram of the *Staphylococcus lugdunensis* isolates.
Flow diagram of the *S. lugdunensis* isolates included for medical chart review.

Materials and Methods

The study design was based on a retrospective case series. Between January 2012 and December 2019, 3733 children were treated at Ehime University Hospital. We retrospectively reviewed all patients with cultures positive for *S. lugdunensis* between January 2012 and December 2019. Children <15 years of age with a positive culture (blood, bile, tissue, sputum/tracheal aspirate, wound/abscess, cerebrospinal fluid [CSF], urine, stool) for *S. lugdunensis* were eligible for study, including medical chart review. The process whereby children were selected for the study is shown in Figure 1.

At first, we focused on the ward, in which *S. lugdunensis* was isolated, and classified study subjects into either the critical care unit group (Group A) or the general medical ward group (Group B). Critical care units were defined as wards that were either PICU, NICU, GCU, and PHCU, whereas general medical wards were wards failing to fulfill the definition of critical care unit.

Moreover, study subjects were classified into having either *S. lugdunensis* infection or *S. lugdunensis* colonization (or contamination); in the latter case, a positive

culture for *S. lugdunensis* was considered not to be clinically significant. For abscess, wound, sputum, tracheal aspirate, stool, and urine cultures positive for *S. lugdunensis*, infection was considered if local or/and systemic symptoms compatible with infection (eg, fever, irritability, poor feeding, tachycardia, tachypnea) were observed in the presence of a positive culture. For blood, CSF, bile, and tissue cultures positive for *S. lugdunensis*, infection was deemed plausible when systemic symptoms were present in addition to a positive culture. Children diagnosed with *S. lugdunensis* infection were retrospectively reviewed.

Healthcare-associated infections were defined as follows: (i) *S. lugdunensis* infection identified more than 48 hours after admission to the hospital; (ii) *S. lugdunensis* infection in a patient fitted with medical devices or indwelling catheters permanently placed *via* the skin at the time of culture; or (iii) *S. lugdunensis* infection in a patient with a history of *S. lugdunensis* infection, hospitalization, surgery, or residence in long-term care facility. Children with *S. lugdunensis* infection with none of the above-mentioned features were classified as having community-acquired infections.⁴

Next, we analyzed selected clinical parameters for each *S. lugdunensis*-infected patients, including age, gender, underlying disease, diagnosed infections, way of infection acquisition, specimen provided for culture, use of implanted medical device, antibiotic treatment, surgical procedure, and clinical outcome. The period of follow-up was 30 days.

Bacterial isolates were identified using Gram staining, standard bacteriological methods (catalase-positive, coagulase-negative, pyrrolidonyl arylamidase-positive, ornithine decarboxylase-positive, and acid production tests for mannitol-negative results), and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry.⁷⁻¹⁰ Antimicrobial susceptibility testing of bacterial isolates was routinely performed using the broth microdilution method.¹¹ Susceptibility was assessed according to the guidelines of the Clinical and Laboratory Standards Institute (M100-S27).¹²

Cefazolin has been the first-choice drug to treat methicillin-susceptible *Staphylococcus* infections because oxacillin and nafcillin are not approved for use in Japan. Accordingly, methicillin resistance was confirmed on the basis of the antibiotic susceptibility results for cefazolin and the presence of the *mecA* gene. We used polymerase chain reaction (PCR) to detect the *mecA* gene.¹³

Informed consent was waived due to the retrospective nature of this study and the fact that we used a de-identified chart review. The methods applied in this study were approved by the University Institutional Review Board.

Statistical Analysis

All statistical analyses were performed using SPSS Statistics for Windows Version 22 (IBM, USA). For univariate analysis of non-normally distributed variables, median values (50th percentile), and interquartile ranges (IQR, 25th-75th percentiles) were used. Fisher's exact probability test or the χ^2 test were performed to analyze categorical data. The Mann-Whitney *U* test was applied to compare the 2 independent samples with regard to age. Differences with a probability (*P*) value <.05 (for 2-sided tests) were considered statistically significant.

Results

A total of 25 children were eligible for study, of whom 19 were classified into Group A and 6 were classified into Group B. Table 1 summarizes the clinical features and laboratory findings of the 25 children with *S. lugdunensis*-positive cultures during the study period.

The children comprised 16 males (64.0%) and 9 females (36.0%) and had a median age of 2 months (IQR, 21 days-2 years). The median age of Group A was 1 month (IQR, 16 days-3.5 months, *n*=16), whereas that of group B was 2 years (IQR, 1.1 years-4.3 years, *n*=9); no significant difference in age was observed between groups A and B (*P*=.997). Underlying diseases included congenital heart disease (*n*=7) and malignancy (*n*=2). There were no significant differences between groups A and B with regard to the presence or type of underlying disease (*P*=.579).

Moreover, insignificant differences were observed for factors such as gender, implanted medical devices, and culture source. Meanwhile, there were significantly more cases of colonization in Group A than in Group B (*P*<.01).

As shown in Table 1, the number of methicillin-resistant *S. lugdunensis* isolates was significantly higher in Group A than in Group B (68.4% vs 0%, respectively; *P*<.01). However, insignificant differences in antibiotic susceptibility to ampicillin, clarithromycin, clindamycin, minocycline, and vancomycin were observed. Moreover, the vancomycin minimum inhibitory concentration for *S. lugdunensis* of 24 of the 25 isolates was <0.5 $\mu\text{g/mL}$, while that of the remaining isolate was 2 $\mu\text{g/mL}$.

Table 2 summarizes the clinical and laboratory findings of the eleven children with *S. lugdunensis* infection who were retrospectively reviewed. These children comprised 7 males (63.6%) and 4 females (36.4%). The median age was 2 years (IQR, 6 months-3.5 years, *n*=11). Underlying diseases included hypoxic ischemic encephalopathy (*n*=1), Dandy-Walker syndrome (*n*=2), brain tumor (*n*=1), hypoplastic left heart syndrome (*n*=1), and preauricular pits (*n*=2). Two patients did not have any underlying disease.

Three patients required central venous catheter (CVC). One patient received ventriculoperitoneal (VP) shunt placement, and 1 patient was subject to cystoperitoneal (CP) shunt placement.

As shown in Table 2, the indications for antibiotic treatment were bacteremia (*n*=2), pneumonia (*n*=1), meningitis (*n*=1), cholangitis (*n*=1), skin and soft tissue infections (SSTI, *n*=5), and lymphadenitis (*n*=1). Patients 3 and 6 were diagnosed with clinically significant bacteremia, because 2 separate blood cultures were positive for *S. lugdunensis*. Additionally, Patient 3 had his peripheral venous catheter removed, and *S. lugdunensis* also grew in the sample collected from the peripheral venous catheter tip. The portal of entry was unclear in Patient 6.

Six patients had healthcare-associated infection, whereas 5 patients had community-acquired infections.

Table 1. Clinical Characteristics and Antibiotic Resistance Data on the *Staphylococcus lugdunensis* Isolates Reviewed in the Current Study.*

	Group A		Group B	P value
	All patients (n=25)	Critical care unit (n=19)	General medical ward (n=6)	
Age (median, IQR)	2 mo (21 dy-2yr)	1 mo (16 dy-3.5 mo)	2 yr (1.1 yr-4.3 yr)	.997
Male	16	12	4	.637
Infection	11	5	6	<.01
Underlying disease	22	17	5	.579
Congenital heart disease	7	7	0	.105
Malignancy	2	0	2	.050
Implanted medical device	11	8	3	.548
Culture source				.126
Blood	2	1	1	
Urine	1	1	0	
Bile	1	1	0	
Lymphoid tissue	1	1	0	
Cerebrospinal fluid	1	0	1	
Stool	1	1	0	
Sputum/Tracheal aspirate	10	10	0	
Wound/Abscess	8	4	4	
Antimicrobial susceptibility [†]				
Ampicillin	21 (84.0)	16 (84.2)	5 (83.3)	.766
Cefazolin	13 (52.0)	13 (68.4)	0 (0)	<.01
Clarithromycin	6 (24.0)	3 (15.8)	3 (50.0)	.125
Clindamycin	5 (20.0)	2 (10.5)	3 (50.0)	.070
Minocycline	0 (0)	0 (0)	0 (0)	—
Vancomycin	0 (0)	0 (0)	0 (0)	—

Abbreviations: dy, day; mo, month; yr, year.

*All data excluded age are presented as the no. (%), unless otherwise stated.

[†]Number of antibiotic resistant (%).

Both cases of *S. lugdunensis* bacteremia reflected healthcare-associated infections. Three isolates (patient 1 through 3) were positive for the *mecA* gene and exhibited methicillin resistance (27%, 3/11); all 3 were seen in healthcare-associated infections.

Seven patients had been subject to surgical procedures, such as drainage for *S. lugdunensis* infection treatment. At the time of the final follow-up, all patients were observed to be healthy without any symptoms attributable to *S. lugdunensis* infection.

Discussion

This study is the first to investigate the clinical and microbial features of *S. lugdunensis* focusing on the ward where the bacteria were isolated from children.

Our data indicate that 76% (19/25) of the *S. lugdunensis* isolates were identified in cultures submitted from critical care units (PICU, NICU, GCU, or PHCU), and there were significantly more cases of colonization

in critical care units than in the general ward units ($P < .01$). We speculated that the relatively high detection rate reflected the fact that surveillance culturing was routine procedure.

German et al¹⁴ reported that only 2.1% (7/347) of CoNS isolates were found to be *S. lugdunensis*, and only 1 isolate (14.3%, 1/7) was considered possibly clinically significant at a pediatric center. They reasoned that *S. lugdunensis* does not appear to be a common pathogen in children. Meanwhile, in our study, 44% (11/25 cases) of the 25 strains reflected infection rather than colonization. Our results suggest that *S. lugdunensis* should be recognized as an important bacterium that can cause invasive infections. The frequency of *S. lugdunensis* infection might be underestimated if general bacterial laboratories do not accurately identify all CoNS species. Accordingly, it is necessary to carefully determine in each individual case whether *S. lugdunensis* is a commensal (colonization or contamination) or an infection.

Table 2. Clinical and Laboratory Findings of Patients With *Staphylococcus lugdunensis* Infection Reviewed in the Current Study.

No.	Age	Sex	Ward [†]	Acquisition	Underlying disease	Specimen	Diagnosis	Device	Antibiotics	Surgical procedure	MR*
1	4 mo	F	Group A	HA	HIE	Sputum/Tracheal aspirate	VAP	None	CLDM, AZM	None	+
2	24 dy	M	Group A	HA	HLHS	W/A	SSTI	CVC	SBT/ABPC	None	+
3	2 mo	M	Group A	HA	DWS	Blood	CRBSI	CPS	MEPM, VCM	None	+
4	6 yr	F	Group A	CA	CBD	Bile	Cholangitis	None	CAZ	Choledocho-jejunostomy	-
5	2 yr	M	Group A	CA	None	Lymphoid tissue	Lymphadenitis	None	CEZ	Lymphadenectomy, drainage	-
6	12 yr	M	Group B	HA	Brain tumor	Blood	Sepsis, FN	CVC	MEPM, VCM	None	-
7	8 mo	M	Group B	HA	DWS	CSF	Meningitis	VPS	MEPM, LZD	Drainage	-
8	2 yr	M	Group B	HA	ALL	W/A	SSTI	CVC	None	Drainage	-
9	5 yr	F	Group B	CA	None	W/A	SSTI	None	CFDN	Drainage	-
10	2 yr	M	Group B	CA	Preauricular pits	W/A	SSTI	None	None	Drainage	-
11	9 mo	F	Group B	CA	Preauricular pits	W/A	SSTI	None	TBPM-PI	Drainage	-

Abbreviation: ALL, acute lymphocytic leukemia; AZM, azithromycin; CA, community-acquired; CAZ, ceftazidime; CBD, congenital biliary dilatation; CEZ, cefazolin; CFDM, clindamycin; CPS, cystoperitoneal shunt; CRBSI, catheter-related bloodstream infection; CSF, cerebrospinal fluid; CVC, central venous catheter; dy, day; DWS, Dandy-Walker syndrome; F, female; FN, febrile neutropenia; HA, healthcare-associated; HIE, hypoxic ischemic encephalopathy; HLHS, hypoplastic left heart syndrome; LZD, linezolid; M, male; MEPM, meropenem; mo, month; MR, methicillin resistance; SBT/ABPC, sulbactam/ampicillin; SSTI, skin and soft tissue infection; TBPM-PI, tebipenem pivoxil; VAP, ventilator associated pneumonia; VCM, vancomycin; VPS, ventriculoperitoneal shunt; W/A, wound/abscess; yr, year.

**mecA* positive.

[†]Group A, critical care unit; Group B, general medical ward.

No studies published so far have investigated in detail the background of pediatric hospitalized patients with *S. lugdunensis* infection. In our study, 9 of the 11 patients had underlying disease. Hence, most patients with *S. lugdunensis* infection had underlying disease, which for instance caused a breakdown of the skin barrier (patients 10 and 11) or required the use of implanted medical devices that disrupted the skin barrier such as CVC, VP-shunt, or CP-shunt (patients 2, 3, 6-8). It is assumed that *S. lugdunensis*, which is a part of the normal human skin flora, invades and causes infectious diseases triggered by the breakdown of the skin barrier, and caution is required for patients with a fragile skin barrier.

Antimicrobial drug resistance is a serious threat to successful antibiotic treatment of hospitalized children with staphylococcal infections. Although the susceptibility of *S. lugdunensis* to penicillin was good in the 1990's, penicillin resistance due to penicillinase production has increased in recent years.¹⁵ In a report from the USA in 2010, penicillin resistance was as high as 45% among 42 strains of *S. lugdunensis*.¹⁶ In the present study, penicillin resistance was even more pronounced, namely 84% (21/25 cases).

Reports on methicillin-resistant *S. lugdunensis* infections are rare and include mainly a few case reports. Pereira and Cunha Mde¹⁷ detected the *mecA* gene in 69 of 100 CoNS strains, including 50% (1 of 2 strains) of the *S. lugdunensis* strains identified. In our study, the methicillin-resistance rate of *S. lugdunensis* was 52% (13/25 cases). Interestingly, resistance to cefazolin was significantly higher in isolates from intensive care units than in isolates obtained from children in the general wards. Recently, Ternes et al¹⁸ reported that among 392 neonates admitted to the NICU, multidrug resistance was detected in 2.2% and 29.9% of the CoNS isolates at admittance and discharge, respectively ($P=.053$). The authors pointed out that NICU represents an environment with an increased risk for colonization by multidrug-resistant CoNS, which might be due to the persistence and/or horizontal spread of methicillin-resistant strains in critical care units.

Meanwhile, Yeh et al¹⁹ reported that a higher proportion of the healthcare-associated isolates than of the community-acquired isolates were resistant to oxacillin (32.1% vs 2.1%, respectively; $P<.001$). In our study, methicillin-resistant *S. lugdunensis* was detected more often in isolates reflecting healthcare-associated infections than in isolates representing community-acquired infections (50% vs 0%, respectively; $P=.064$). Hence, we observed a tendency of methicillin resistance abounding in the healthcare-associated infections. *S. lugdunensis* healthcare-associated infections may involve an increased risk of severe invasive infections such as bacteremia, sepsis, or bacterial meningitis.

Therefore, it is especially important to select appropriate antibiotics for treatment. The use of anti-methicillin-resistant *S. aureus* agents should be considered in cases of *S. lugdunensis* infection in critical care units or healthcare-associated infections until antimicrobial susceptibility results are known.

On the other hand, in the general ward, no strain resistant to cefazolin was observed (0%), and cases of SSTI represented most of the infectious diseases in our study. Moreover, methicillin resistance was not observed in the children with community-acquired infection (0/5 cases). Therefore, *S. lugdunensis* infection in the general ward or community-acquired *S. lugdunensis* infection may currently be treated with cefazolin or oxacillin.

Our study on pediatric patients with *S. lugdunensis* revealed that the bacteriological characteristics of *S. lugdunensis* differ depending on the background of the patients, such as the type of ward to which they have been admitted. These results suggest that consideration of the patient's background may be critical to selecting the appropriate antibiotic therapy.

The limitations of our study include its retrospective nature, the fact that it was performed at a single center, and the small sample size. Moreover, the study may not universally reflect the clinical features of *S. lugdunensis* infection in children. Finally, molecular epidemiological analysis by multi-locus sequence typing or pulsed-field gel electrophoresis analysis was not been carried out. As *S. lugdunensis* infection in pediatric patients is rare, accumulation of cases is required to confirm our findings.

Conclusion

Our study suggests the need for caution regarding methicillin-resistant *S. lugdunensis*, which may cause severe invasive infection in pediatric patients at critical care unit.

Author Contributions

F.O., H.T., M.K. and J.H. managed the patient and prepared the manuscript. S.M. and H.M. performed microbiological analysis. M.E. and M.EI. reviewed the manuscript. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics and Consent

Informed consent was waived due to the retrospective nature of this study and the fact that we used a de-identified chart review. The methods applied in this study were approved by the Ehime University Institutional Review Board (Approval #: 1902008).

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