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Original article

Frequency, clinical manifestations, and outcomes of *Staphylococcus lugdunensis* Bacteremia in children

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ABSTRACT

Background: *Staphylococcus lugdunensis* (*S. lugdunensis*) is known as a common cause of clinically significant infections in adults although the clinical importance of *S. lugdunensis* isolates from pediatric samples is less known. The aim of this study is to assess the incidence, characteristics, and outcomes of *S. lugdunensis* bacteremia (SLB) in children.
Methods: From January 2009 to March 2014, all blood culture isolates were retrospectively screened for *S. lugdunensis*. We analyzed the isolates for antimicrobial susceptibility and patients who had developed SLB by reviewing the electronic medical records. Additionally, we identified *mecA* and *blaZ* for available isolates by polymerase chain reaction (PCR).
Results: Of the 647 positive blood cultures during the period, 277 (42.8%) yielded coagulase negative *Staphylococcus* (CoNS), and 10 of 277 CoNS were *S. lugdunensis* (3.6% of all CoNS isolates). Of eight SLB episodes identified, seven (87.5%) were considered to have clinically significant bacteremia. All patients had underlying diseases, and all SLB were either healthcare-associated or hospital acquired. There was no infectious endocarditis (IE) development. All patients were treated with antibiotics and recovered without sequelae. We found that the isolates in our study showed higher antibiotic resistance to penicillin (8/8: 100%) and oxacillin (6/8: 75.0%) than previously reported. Among isolates available, we detected *mecA* in all four isolates resistant to oxacillin and *blaZ* in 5 of 6 isolates resistant to penicillin.
Conclusions: *S. lugdunensis* is a rare but an important cause of bacteremia in children.

1. Introduction

Staphylococcus lugdunensis (*S. lugdunensis*), first described in 1988 [1], is present as a normal skin commensal in healthy individuals. The organism is now known to be one of the most virulent coagulase negative *Staphylococcus* (CoNS) because of its ability to produce some virulence factors [2]. Available studies on the pathogenesis of *S. lugdunensis* describe the characterization of these virulence factors including the delta toxin-like hemolytic peptides, von Willebrand factor-binding protein (vWbl), fibrinogen-binding protein (Fbl), autolysin (AtlL), iron-regulated surface determinant proteins (Isd), and sortase A [2–6]. In addition, *S. lugdunensis* is known to form biofilm, such as *Staphylococcus aureus* (*S. aureus*) and other CoNS. While some factors contributing to biofilm formation of *S. lugdunensis* are well-known to have homologs in other staphylococci, a recent study reports *S. lugdunensis* can form biofilm in a different manner [7,8]. Although the mechanism remains almost unclear, an ability of *S. lugdunensis* to form biofilm may contribute to its virulence.

Although the organism is often biochemically identified, it can be positive by slide coagulase or latex agglutination tests which can be confused with those of *S. aureus*. In addition, its colony morphology, pigmentation, and hemolysis often vary between strains, which is also confusing. Thus, *S. lugdunensis* is sometimes difficult to identify accurately in a clinical laboratory.

Several reports of adult patients demonstrated that CoNS often causes infectious endocarditis (IE) [8–11]. Recently, *S. lugdunensis*

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has also been known to be a common cause of bone and joint infections, skin and soft tissue infections, urinary tract infections, and central nervous system infections in adult [12,13]. On the other hand, there are few reports about pediatric *S. lugdunensis* infections [14]. Therefore, more systematic studies of *S. lugdunensis* infections solely in the pediatric population are important to elucidate its clinical significance when *S. lugdunensis* is isolated from pediatric clinical specimens, particularly from blood cultures. The aim of this study is to explore the frequency, clinical manifestations, and outcomes of *S. lugdunensis* bacteremia (SLB) patients in a tertiary pediatric hospital.

2. Materials and methods

2.1. Study design and patient population

The microbiological records of all *S. lugdunensis* blood isolates in the computerized database of the Nagano Children's Hospital were retrospectively reviewed. This hospital has 180 inpatient beds and approximately 80,000 annual visits for outpatients. Patients with one or more blood cultures positive for *S. lugdunensis* were further analyzed by electronic medical record review. We explored patient characteristics, results of cultures, diagnosis of infections, treatments, and clinical outcomes. The study period was from January 2009 to March 2014.

2.2. Definition

SLB was defined to be clinically significant in patients with three conditions; two or more separate blood cultures were positive, one blood culture and another culture were positive or one blood culture was positive and a systemic inflammatory response syndrome was present without any other assumed causes. We considered SLB as coincidental in other conditions.

The category of infection was defined as follows: (1) healthcare-associated: infection which occurs within 48 h of admission if the patient received specific home care or attended a hospital or hemodialysis clinic in the 30 days before the infection, if the patient was hospitalized two or more days in the 90 days before infection or if the patient resided in a nursing home, (2) hospital-acquired infection which occurs more than 48 h after admission, (3) community-acquired infection which fulfills the definition of neither healthcare-associated nor hospital associated. The diagnosis of IE was based on the modified Duke criteria [15].

2.3. Microbiology

Blood cultures were processed by the automated blood culture analyzer (BACTEC FX; Becton Dickinson Diagnostic Instrument System, Franklin Lake, NJ, USA). Other cultures were processed by conventional methods. Identification of clinical isolates and determination of minimal inhibitory concentration (MIC) were performed using pos combo 3.1J panels (Beckman Coulter Inc., Brea, USA) in the automated MicroScan WalkAway system (Beckman Coulter Inc.). Susceptibility of isolates was interpreted according to the Clinical and Laboratory Standards Institute (CLSI) M100-S22 criteria [16].

Molecular identification of strains by sequencing 16S rRNA was used for reconfirmation tests if strains were stored for culture collection. The gene coding for mecA and blaZ in the isolate was detected by polymerase chain reaction (PCR). The *mecA* gene was examined when a strain was resistant to oxacillin and the *blaZ* gene was also examined as when a strain was resistant to penicillin. These molecular procedures were performed as previously described [17–19].

3. Results

In 15,921 admissions during the study period, seven patients had eight episodes of SLB. Of the eight episodes, seven were considered to be clinically significant bacteremia (87.5%, incidence; 4.4 per 10,000 admissions). Of the 647 positive blood cultures during the period, 277 (42.8%) were CoNS, and 10 of the 277 CoNS were *S. lugdunensis* (3.6% of all CoNS isolates) (Table 1). Only one isolate was considered to be contamination detected from a 16-year-old girl who had hypoxic-ischemic encephalopathy. She was admitted to our hospital for the treatment of aspiration pneumonia, and *S. lugdunensis* grew from one of the blood cultures after admission. She was treated with ampicillin/sulbactam, to which the isolate was not susceptible, and recovered without any problem.

The clinical characteristics of the seven SLB patients are shown in Table 2. Patients 1 and 2 were the same patient with dermatomyositis. He was treated for first SLB without removal of his central venous catheter (CVC). However, 6 months after the episode, he had SLB again followed by removal of the CVC resulting in approximately one year of catheterization. All patients except patient 4 had SIRS with one or two positive blood culture and met the clinically significant SLB definition. Although SIRS was not present in patient 4 with hypoxic ischemic encephalopathy, her spasms and marked peripheral coldness remarkably deteriorated. Two separate blood cultures at that time were positive for *S. lugdunensis*, which made diagnosis of clinically significant SLB. The portal of entry was unclear.

Their median age was 3 years and 1 month old (range, 2 months to 5 years and 11 months), and three (42.9%) were female. All patients had underlying diseases and received some surgical procedures. All SLB were healthcare-associated or hospital acquired. No IE was found. The entries of SLB were via a CVC in three (42.9%), mediastinitis in two (28.6%), artificial vessel infection in one (14.3%), and of unknown origin in one. All patients were treated with antibiotics and all patients except case 1 received catheter removal or surgical debridement. They recovered without sequelae.

The distribution of antimicrobial susceptibilities of each isolates is summarized in Table 3. One patient had two different isolates in the same SLB episode (patient 4). We considered it a microbial substitution and a total of eight isolates were included in seven SLB patients. In the eight isolates, all were resistant to penicillin, six were resistant to oxacillin (75.0%), and three were resistant to erythromycin (37.5%). However, all isolates were susceptible to vancomycin and sulfamethoxazole-trimethoprim.

We analyzed 6 of 8 strains for molecular reference methods, which were obtained from patients 3–7. Four of six isolates were resistant to oxacillin. All six isolates available were reconfirmed as

Table 1
Isolates detected from blood cultures during the study period.

Isolate	*n*
CoNS	277
S. epidermidis	158
S. hominis	20
S. haemolyticus	20
S. intermedius	16
S. capitis	16
S. lugdunensis	**10**
S. warneri	4
S. simulans	2
Difficult to identify	27
Other pathogens	370
Total	647