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# The occurrence of infective endocarditis with *Staphylococcus lugdunensis* bacteremia: A retrospective cohort study and systematic review

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## KEYWORDS

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**Summary** *Background:* *Staphylococcus lugdunensis* is a coagulase-negative staphylococcus with similar virulence characteristics as *Staphylococcus aureus*. Whether *S. lugdunensis* causes infective endocarditis (IE) in a similar proportion of cases as *S. aureus* (reported to be 12.6% in a definitive multicenter prospective study) is unclear.

*Methods:* We conducted a retrospective cohort study of adult patients with at least one blood culture positive for *S. lugdunensis* at our institution from January 2006 to December 2014. We examined microbiology data, ascertained disease severity and determined the proportion of patients with definite or possible IE based on the 2000 Modified Duke Criteria. Because coagulase-negative staphylococci were routinely identified to the species level at our institution from 2012 onwards, we determined the proportion of patients with definite or possible IE before and after implementation of routine speciation. We also compared our results with reported proportions of IE among patients with *S. lugdunensis* bacteremia (SLB) in other institutions by conducting a systematic review of the scientific literature. Nonparametric bootstrapping methods were performed to determine 95% confidence intervals (CI) for proportions of IE in patients with SLB.

*Results:* Seventy-four patients with SLB were identified, of whom 64% (47/74) had sepsis by SIRS criteria, and 18% (13/74) had severe illness by Pittsburgh bacteremia score (PBS). Kaplan–Meier survival analysis showed that one-year survival among patients with severe illness was worse than patients with non-severe illness ( $p = 0.02$ ). Fifteen percent (11/74) of patients had definite or possible IE (95% CI 6.8–23.0%). The proportion of SLB patients with definite or possible IE was 15.8% (6/38, 95% CI 5.3–28.9%) prior to routine speciation and 13.9% (5/36, 95% CI 2.8–27.8%) after routine speciation ( $p = 0.71$ ). Among patients with at least two positive

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blood cultures for *S. lugdunensis*, 25% (10/40, 95% CI 12.5–40.0%) had IE. Systematic review of the literature yielded eight relevant retrospective studies. Of studies that included patients with one or more positive blood cultures for *S. lugdunensis*, the proportion of IE ranged from 6.3% to 27.0%.

**Conclusion:** The proportion of definite or possible IE among patients with SLB is similar to the proportion of IE among patients with *S. aureus* bacteremia. The proportions of IE among patients with SLB at other institutions fall within the 95% CI yielded by bootstrapping. Our findings suggest that growth of *S. lugdunensis* in two separate blood cultures should prompt consideration of workup for IE.

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## Introduction

*Staphylococcus lugdunensis* is a coagulase-negative staphylococcus (CNS) that can cause aggressive tissue-invasive infections similar to *Staphylococcus aureus*.<sup>1–3</sup> It has been described as a causative agent of skin and soft tissue infections, bone and joint infections, urinary tract infections, bloodstream infections and infective endocarditis (IE).<sup>1,4</sup> *S. lugdunensis* IE can present with rapid valve destruction and abscess formation, and high mortality.<sup>5,6</sup> It binds to von Willebrand factor, which can explain its ability to adhere to cardiac valves and blood vessel walls.<sup>7</sup> Moreover, it is the only other staphylococcal species apart from *S. aureus* that harbors a locus of genes encoding proteins involved in iron acquisition from hemoglobin, which enhances its virulence.<sup>8</sup> According to the Infectious Diseases Society of America (IDSA), IE should be ruled out in cases of *S. aureus* bacteremia (SAB), and the Modified Duke Criteria for Endocarditis includes *S. aureus* in two separate blood cultures as a major criterion for IE.<sup>9</sup> Whether the same guidelines should be applied to *S. lugdunensis* given its comparable virulence to *S. aureus* is unclear.

*S. lugdunensis* IE is uncommon and was reported to cause only 1.1% of IE cases in a prospective cohort study from Spain.<sup>10</sup> Because of its relative rarity, only a few small epidemiologic studies of SLB have been conducted, and the proportion of patients with SLB who have IE is not well-defined given differences in cohort inception and definitions of IE.<sup>11–14</sup> In contrast, SAB is well-studied, with the most recent prospective cohort study reporting that 12.6% of patients with SAB had IE based on standard definitions using the Modified Duke Criteria.<sup>15</sup> Whether the proportion of IE among patients with SLB is comparable to reported proportions of IE among patients with SAB is unclear.

To determine whether the proportion of IE among patients with SLB is comparable to reported proportions of IE among patients with SAB, we retrospectively reviewed all SLB episodes at Barnes-Jewish Hospital/Washington University from 2006 to 2014, and conducted a systematic review of the scientific literature to identify the proportion of IE in patients with SLB reported in other institutions. Understanding the epidemiology of SLB and knowing the proportion of IE among patients with SLB will improve the management of this potentially deadly pathogen.

## Methods

### Retrospective review

#### Study design and cohort inception

We conducted a retrospective chart review of patients aged 18 years and older with SLB admitted to Barnes-Jewish Hospital/Washington University from January 2006 to December 2014. SLB was defined as isolation of *S. lugdunensis* in at least one blood culture bottle. We identified 75 patients with SLB using the Barnes Medical Informatics Database, and excluded one patient because his chart was not available for review. Demographic and clinical characteristics for the cohort were determined at the onset of bacteremia, which was defined as the date of the first positive blood culture. The research protocol of this study was approved by the Washington University Institutional Review Board with IRB number 201504015.

#### Microbiology

The Barnes-Jewish Hospital microbiology laboratory used the VersaTREK system for processing of blood cultures for the duration of this study. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF) was the primary method of identifying bacteria from 2012 onward.<sup>16</sup> As a result, species-level identification of all coagulase-negative staphylococci and reporting of *S. lugdunensis* became routine in 2012. Prior to this, biochemical identification systems were used. Antimicrobial susceptibilities were performed using disk diffusion method and interpretation was based on clinical breakpoints from the Clinical and Laboratory Standards Institute (CLSI) guidelines.<sup>17</sup>

#### Definitions

IE was defined according to the 2000 Modified Duke Criteria.<sup>9</sup> Definite and possible endocarditis were included as cases. The severity of illness was assessed using the Pittsburgh bacteremia score (PBS) and systemic inflammatory response syndrome (SIRS) criteria by the surviving sepsis campaign.<sup>18</sup> PBS (based on points assigned for vital signs, need for mechanical ventilation, occurrence of cardiac arrest, and mental status change at the time of positive blood culture), was validated in multiple observational studies for both Gram-negative and Gram-positive bacteremia, including *S. aureus* and *S. lugdunensis*.<sup>19–25</sup> Severe bacteremic illness was defined as a PBS score of >4.

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