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BRIEF REPORT

Identification of the Skip Phenomenon Among Patients With *Staphylococcus lugdunensis* Infective Endocarditis: A Retrospective Review

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The skip phenomenon (SP) is a pattern where blood cultures are intermittently positive before final clearance. We report that one-third of patients with *Staphylococcus lugdunensis* infective endocarditis experienced the SP. Patients with the SP experienced both a longer duration of bacteremia and hospital stay, with a higher 1-year mortality rate.

Keywords. bacteremia; blood culture; infective endocarditis; skip phenomenon; *Staphylococcus lugdunensis*.

Staphylococcus lugdunensis is a coagulase-negative *Staphylococcus* and is well-recognized as a cause of an aggressive and complicated infection in patients akin to that caused by *Staphylococcus aureus* [1]. This includes cardiovascular infections, where rates of 30-day mortality can be more than double that caused by *S aureus* [2].

The skip phenomenon (SP) is a blood culture pattern that has been described in *S aureus* bacteremia (SAB) where a patient with negative blood cultures on early antibiotic treatment develops positive blood cultures [3]. SP was initially recognized due to the common practice of repeating blood cultures to insure clearance of SAB [4]. Moreover, its occurrence does not appear to be related to appropriate antibiotic selection or its dosing. While the SP has been described in SAB, it has not been described in *Staphylococcus lugdunensis* bacteremia (SLB). Given the similarly aggressive nature of *S lugdunensis* and *S aureus*, we retrospectively reviewed patients with *S lugdunensis* infective endocarditis (IE) seen at Mayo Clinic Enterprise sites for the occurrence of the SP in patients with *S lugdunensis* IE.

METHODS

We conducted a multisite (Mayo Clinic Enterprise including campuses at Arizona, Florida, Minnesota, and the Mayo Clinic Health System in the Upper Midwest), retrospective study of all patients diagnosed with *S lugdunensis* IE between 1 June 2012 and 30 June 2022. At least 2 blood culture sets were collected from each patient. The Becton Dickinson BD BACTEC FX platform was used for each blood culture set, which consisted of 1 BD BACTEC lytic Anaerobic/F bottle and 2 BD BACTEC Plus Aerobic/F bottles with 120 hours of incubation. Time to positivity (TTP) was defined by the time the platform identified growth in any bottle. If BC bottles flagged positive on the BD BACTEC FX platform, then Gram staining and subculturing onto appropriate media were performed. Isolates underwent phenotypic antimicrobial susceptibility testing by agar dilution, and Clinical and Laboratory Standards Institute guidelines were used to interpret minimum inhibitory concentration [5].

We defined the SP similarly to that previously reported for *S aureus* [3]. SLB was defined as having at least 1 positive blood culture for *S lugdunensis*. The SP was defined as recurrence of bacteremia after blood cultures had been negative for 24 hours —for example, a patient having positive blood cultures on hospital day 1, then no growth for at least 24 hours on day 2, then positive cultures when repeated on day 3. Thus, only patients who had cultures repeated after a negative culture could be defined as displaying the SP. TTP was defined as the mean of all positive blood cultures from a given day. We averaged the TTP on the initial day of diagnosis and on the first day after this. IE was defined based on modified Duke criteria [6].

We recorded patient age at diagnosis, sex, body mass index (BMI), presence of cardiac prosthetic devices, and both in-hospital and 1-year mortality. We recorded diagnoses to determine Charlson comorbidity index scores [7]. Data on initial TTP of cultures growing *S lugdunensis*, duration of bacteremia, length of hospitalization, and whether patients underwent surgery or were transferred to an intensive care unit were abstracted.

Given the small sample size expected, only descriptive statistics are reported. The Mayo Clinic Institutional Review Board deemed this study exempt.

RESULTS

Overall, 18 cases of *S lugdunensis* IE were identified. Fifteen of the 18 patients had sufficient repeated cultures to determine SP.

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The median age was 71 (range, 34–91) years (interquartile range, 63–81 years) and 80% were men. Median BMI was 29.3 (range, 23.6–49.6) kg/m^2. Median duration of bacteremia was 6 (range, 4–9) days in the SP group and 2 (range, 1–5) days in the non-SP group. Four (26.7%) patients died due to IE, 2 (13.3%) of them during their hospitalization for IE. Overall, 40% of patients died within a year of *S lugdunensis* IE diagnosis.

In 14 of the 15 cases, blood cultures were repeated within 24 hours of a positive culture. Five (33%) demonstrated SP and are described in Table 1. Three of the 5 died within 1 year of obtaining the first blood culture, and 3 were admitted to the intensive care unit. Total hospital length of stay ranged from 5 to 22 days. Initial isolates from all cases tested were susceptible to oxacillin (16/16), vancomycin (17/17), daptomycin (13/13), and linezolid (7/7). The median number of culture sets obtained from those demonstrating SP was 14 (range, 11–20), compared to 9 for those not demonstrating SP (range, 4–15). In 4 of the 5 patients, there were 2 negative culture sets during the SP; in the other, there was 1 negative culture set.

Median hospitalization duration was 18 (range, 5–22) days for those with the SP, as compared to 12.5 (range, 6–91) days for those without the SP. The median initial time to positivity was 20.75 (range, 16–23.5) hours for cases demonstrating the SP and 18 (range, 13–31.5) hours for other cases. The median TTP for second positive cultures was 28 (range, 21–88) hours for cases demonstrating the SP and 28.5 (range, 20–45) hours for cases without the SP but with persistent growth of *S lugdunensis*.

DISCUSSION

In our retrospective analysis, the SP was identified and affected a high percentage of patients with *S lugdunensis* IE. While our cohort size was small, the 33% rate of the SP is remarkable and indicates a need for clinicians to be aware of the SP. Without repeated blood cultures, date of clearance would have been misinterpreted, potentially leading to contamination of prematurely placed central venous access or cardiac devices. This diagnostic premature closure may also result in delay for a search of metastatic sites of infection. Of note, this rate was greater than that reported in cases of *S aureus* IE, which was reported to be 12% of cases [3].

There are currently no guidelines for treatment of SLB. The most recent guidelines for treatment of SAB do not define the number of negative blood culture sets to determine bacterial clearance, though these were written prior to the most recent characterization of SP [3, 8]. We recommend a strategy to repeat blood cultures daily until all sets from 1 day are negative for 48 hours prior to discharge or placement of longer-term intravenous access. The incubation of additional sets of cultures will be crucial to identify SP, which may necessitate further diagnostic assessment.

Table 1. Clinical Characteristics of Patients With the Skip Phenomenon in *Staphylococcus lugdunensis* Infective Endocarditis

Age (y), Sex	Initial TTP, h	2nd Set of Culture TTP, h	TTP Ratio	Duration of Bacteremia/Duration of Skip, d	Duration of Positive Cultures Before Skip	PREDICT Score (Day 1)	Duration of Antimicrobial Therapy, d	Hospital LOS, d	ICU Admission	1-Year Mortality	Treatment at Time of SP	Comment
91, F	16	88	5.5	5/2	3	2	5	5	No	Yes	Nafcillin, rifampin	Discharge to hospice due to endocarditis
64, M	19.5	28	1.4	6/2	3	2	18	18	Yes	Yes	Cefazolin, levofloxacin	Native bicuspid AV endocarditis with septic emboli
61, M	23.5	26	1.1	7/1	4	4	50	11	No	No	Cefazolin	Native bicuspid AV endocarditis and ICD infection
87, M	21	21	1	4/1	2	5	42[a]	22	Yes	Yes	Cefazolin	Case transferred for IE, unclear culture results from transferring facility
72, M	22	30	1.36	9/3	5	2	42[a]	20	Yes	No	Cefazolin	Native AV/MV endocarditis with diskitis, osteomyelitis, and CNS emboli Persistent bacteremia after change to nafcillin given CNS emboli

Abbreviations: AV, aortic valve; CNS, central nervous system; ICD, implated cardiac defibrillator; ICU, intensive care unit; IE, infective endocarditis; LOS, length of stay; MV, mitral valve; PREDICT, Predicting Risk of Endocarditis Using a Clinical Tool; SP, skip phenomenon; TTP, time to positivity.

[a]Indicates patient placed on lifelong suppression after treatment course.

Our study was limited by the small number of patients with *S lugdunensis* IE. Additionally, cases where blood cultures were not repeated may have been less sick-appearing to clinicians and less likely to have serial blood cultures ordered. Duration of bacteremia prior to presenting for blood cultures cannot be defined, and thus time from initial bacteremia to antibiotics is unknown. Mortality outcomes may be incomplete if some of the patients died outside of the Mayo system, though it appears most had healthcare visits after the 1-year cutoff.

The SP appears to be common in patients with SLB with IE. Recognition of this association is important as patient management decisions are considered. There is a chance that *S lugdunensis* could be misinterpreted by some clinicians as an organism of low significance, leading to delayed treatment and subsequent dissemination. Further investigation with a larger cohort of patients with *S lugdunensis* IE and SLB is needed to identify whether treatment delays are a cause of SP, and whether the SP is as prevalent and as relevant in patients with bacteremia but without IE.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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