CJC Open 4 (2022) 474–478

Original Article

Staphylococcus lugdunensis Endocarditis: Lower Mortality in the Contemporary Era?

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ABSTRACT

Background: ***Staphylococcus lugdunensis*** **is a virulent coagulase-negative** ***Staphylococcus*** **that is a rare cause of infective endocarditis (IE) associated with high mortality. A linear growth of IE has occurred over the past several years in Saskatchewan, with overlapping epidemics of human immunodeficiency virus (HIV)/hepatitis C virus driven by injection drug use (IDU). We hypothesized that given the unique challenges faced by our population with IDU and inequitable healthcare access, our cases of** ***S. lugdunensis*** **IE might differ from those in the published literature.**

RÉSUMÉ

Contexte : ***Staphylococcus lugdunensis*** **est un staphylocoque à coagulase négative virulent qui, à de rares occasions, est à l'origine de l'endocardite infectieuse associée à une mortalité élevée. Une augmentation linéaire des cas d'endocardite infectieuse a été observée au cours des dernières années en Saskatchewan, accompagnée d'une épidémie d'infections par le virus d'immunodéficience humaine (VIH) / virus de l'hépatite C liées à l'utilisation de drogues injectables. Nous avons formulé l'hypothèse qu'en raison des difficultés particulières auxquelles doit faire face notre population qui**

Staphylococcus lugdunensis is a rare cause of infective endocarditis (IE) with an estimated mortality rate of 40%-70%.[1,2] In Saskatchewan, our incidence of IE cases in general, and corresponding hospital admissions, has increased linearly over the past 10 years, outpacing population growth.[3] This trend is of particular concern, as IE is associated with high in-hospital mortality and prolonged hospital stays.[3] Moreover, Skinner et al. describe a rise in hepatitis C and human immunodeficiency virus (HIV) infection in Canada that is disproportionately affecting Saskatchewan due to high levels of injection drug use (IDU) and marginalized populations with poor access to healthcare.[4] This combination of findings, coupled with the known fact that hepatitis C and HIV coinfection in IE leads to poorer prognosis,[5] led us to question whether our *S. lugdunensis* IE population had unique clinical characteristics, compared to populations in previous reviews.

S. lugdunensis is a commensal organism that is part of the normal human skin flora.[1] Although it is a coagulase-negative *Staphylococcus* (CoNS), it is unusual in its virulence and pathogenic potential.[1,2,6,7] Skin and soft tissue infections make up the majority of *S. lugdunensis* infections, and oral, ocular, peritoneal, urinary, bloodstream, joint, and central nervous system infections also occur.[1] Based on several studies,[8-12] the incidence of IE among patients with a positive *S. lugdunensis* blood culture is between 6.3% and 27%, with higher ranges associated with persistently positive blood cultures. This incidence is similar to that of the highly virulent *Staphylococcus aureus,* which is associated with IE in at least 12% of patients with bacteremia.[12] In fact, *S. lugdunensis* is often compared to *S. aureus,* owing to the fact that they have some common virulence factors, such as adhesion factors and the ability to form biofilms.[1]

In contrast to other coagulase-negative *Staphylococci* that more commonly affect prosthetic valves, *S. lugdunensis* tends to infect native valves and can be associated with valvular destruction, abscess formation, and metastatic infection.[1,13,14] In fact, in clinical practice, *S. lugdunensis* can behave as aggressively as *S. aureus*.[12] Although it is usually pan-sensitive to penicillins,[1] the propensity of *S. lugdunensis* to cause invasive infection should prompt early consideration for

Received for publication October 13, 2021. Accepted January 26, 2022.

Ethics Statement: The study was approved by the University of Saskatchewan Biomedical Research Ethics Board, and the need to obtain informed consent was waived. Patients and the public were not involved in the design or reporting of this article.

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See page 477 for disclosure information.

https://doi.org/10.1016/j.cjco.2022.01.009

Methods: We retrospectively reviewed the cases of *S. lugdunensis* endocarditis admitted at our tertiary care hospitals in Saskatoon over a 6-year period and analyzed their baseline characteristics, antimicrobial susceptibility data, management, and outcome data, where available, for each patient.

Results: Of the 24 blood cultures positive for *S. lugdunensis,* as identified by our laboratory, we verified 6 cases of definite IE, and 2 cases of probable IE, applying the modified Duke's criteria. A total of 5 of 8 cases involved native valves, with only 1 infection of the bioprosthetic mitral valve, seen in patient with IDU. A total of 5 of 8 cases involved the left-sided valves, with 1 of 8 involving the tricuspid valve. Only 1 death was recorded.

Conclusions: The male predominance and primarily left-sided valve infection we noted in our review were similar to results in the published literature. We noted a lower rate of surgical intervention and mortality than previously observed, which merits further study. We did not find coinfection with HIV and/or hepatitis C virus as an epidemiologic risk factor, likely owing to the low rate of IDU in our study.

Méthodologie : Nous avons étudié de façon rétrospective les cas d'endocardite liée à *S. lugdunensis* admis à nos hôpitaux de soins tertiaires à Saskatoon sur une période de six ans et nous avons analysé leurs caractéristiques initiales, les données relatives à la sensibilité aux antimicrobiens, la prise en charge et les résultats, lorsqu'ils étaient disponibles, pour chaque patient.

Résultats : Parmi les 24 cultures sanguines ayant donné un résultat positif pour *S. lugdunensis,* selon l'évaluation de notre laboratoire, nous avons vérifié six cas confirmés et deux cas probables d'endocardite infectieuse, en utilisant les critères de Duke modifiés. Parmi ces huit cas, cinq impliquaient les valves du côté gauche d'origine, mais seulement un cas d'infection impliquait une bioprothèse de la valve mitrale (chez un patient faisant usage de drogues injectables). Toujours parmi ces huit cas, cinq impliquaient les valves du côté gauche; un impliquait la valve tricuspide. Seulement un décès a été signalé.

Conclusions : La prédominance chez les hommes et l'infection touchant principalement les valves du côté gauche correspondaient aux résultats décrits dans les études publiées. Nous avons noté un taux réduit d'interventions chirurgicales et de mortalité par rapport aux observations antérieures, ce qui mérite une étude approfondie. Nous n'avons pas établi qu'une co-infection par le VIH et/ou le virus de l'hépatite C était un facteur de risque épidémiologique, probablement en raison du faible taux d'utilisation de drogues injectables dans notre étude.

surgical management.[13,14] Of note, to our knowledge, no cases of *S. lugdunensis* IE have been related to IDU. Thus, we also hoped to add more cases to the literature for the purpose of providing a larger sample for further analyses, as suggested by Liu et al.[2] in their comprehensive review of the literature.

Methods

We conducted a retrospective chart review of all patients > 18 years of age who had blood cultures positive for *S. lugdunensis* in the preceding 6 years (2013-2018) and were admitted to one of our 2 main local hospitals. The laboratory database included 1 large tertiary academic hospital and 1 large tertiary community hospital.[15] These hospitals are both located in Saskatoon and service the northern half of Saskatchewan. We systematically gathered information, using our data collection tool (see Supplemental Appendix S1). We identified which of these patients met possible or definite criteria for infective endocarditis based on the modified Duke criteria.[12] We gathered the following information: demographic characteristics; admitting and discharge diagnoses; likely portal of entry; first 5 listed comorbidities obtained from the health record; hepatitis C and HIV status; endocarditis location and characteristics of valves involved; presence of an indwelling device (eg, pacemaker); echocardiographic characteristics; penicillin/oxacillin/vancomycin susceptibility; management strategy; and outcome. Information regarding length of stay and need for intensive care unit services were also collected. Mortality will be compared to that in our general IE population and to that in the published literature.[16,17]

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Results

Of the 24 blood cultures positive for *S. lugdunensis* that were identified in the database, 3 were excluded from the chart review. Two patients were not hospitalized, making clinical details unavailable, and 1 patient's blood culture was erroneusouly included by the laboratory. This exclusion process left 21 patients who underwent chart review, which identified 6 patients with definite IE, and 2 patients with possible IE (see Fig. 1). Demographic information, important comorbidities, and clinical characteristics are outlined by case in Table 1 and summarized in aggregate in Table 2. None of the patients had HIV or hepatitis C coinfection, and none had pacemaker-related infections. A total of 75% of patients had vegetations as seen on transthoracic echocardiography, and the valves involved are described in Table 1. Patient #7 met 1 major and several minor criteria for endocarditis, but the more likely source of his bacteremia was an indwelling vascular catheter. As an echocardiogram was not performed, it is not possible to rule out concomitant IE.

One patient had mitral prosthetic valve infection (12.5% of sample). He had a bioprosthetic mitral valve *S. lugdunensis* vegetation, concomitant IDU, and he died in the intensive care unit after being deemed a nonsurgical candidate. Given that this death was the only one, the overall mortality of our sample was 12.5% (1 of 8). The majority (6 of 8) of *S. lugdunensis*

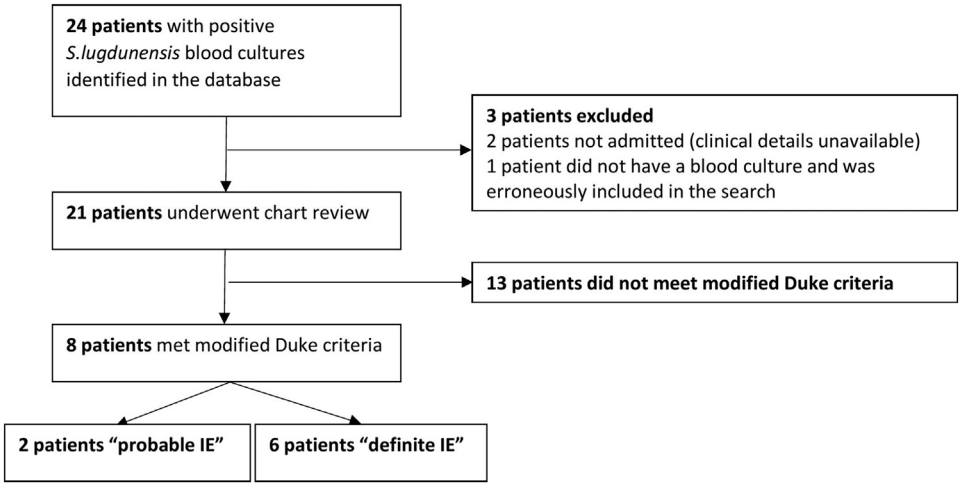

Figure 1. Chart review process: a total of 24 charts were identified as potential infective endocarditis (IE) cases based on our database records of *Staphylococcus lugdunensis* bacteremia. Of these, 3 cases were excluded, as outlined above, leaving 21 charts to review in detail. Of these, 13 patients were excluded as they did not meet the minimum requirement of "probable IE" per the modified Duke criteria.[12] The remaining 8 cases were used in our analysis.

isolates were susceptible to penicillin. One isolate was not reported, and the other was penicillin-resistant, with a minimum inhibitory concentration (MIC) > 0.5, and oxacillin-resistant (MIC > 4), but sensitive to vancomycin (MIC < 0.5).

Discussion

Our clinical review of 8 cases of *S. lugdunensis* endocarditis demonstrated an in-hospital mortality of 12.5%, compared to 21% in both our general IE population and the published literature.[3,16,17] These 8 cases represented 1.3% of our total number of admitted endocarditis cases over the same time frame.[3] Furthermore, among definite cases, 16.7% of patients (1 of 6) had infected prosthetic valves. Both of the surgically managed patients had large vegetations ($>$ 20 mm) and successful valve replacements. The medically managed patients also had good outcomes when they did not have traditional surgical indications for IE.[13]

The most comprehensive recent review of *S. lugdunensis* IE was done by Liu et al.[2] in 2010. The patients in their cohort were

Table 1. Clinical characteristics, management, and outcomes

Age, y	Sex	Comorbidities	Valve involved, clinical presentation	Complications	Management
33	M	History of MV IE ×2, prosthetic MVR, chronic pancreatitis, active IDU, depression	MV involved, 27-mm vegetation	ICU admission, persistent bacteremia, shock	Not surgical candidate, started on cloxacillin until death
42	F	PE, DM, anxiety	TV involved, 10-mm vegetation, presented with bacteremia	Persistent bacteremia, lung emboli	No surgery; started on vancomycin planned for 6 wk, actual duration unknown
44	F	MS, mixed CTD, ILD, chronic pancreatitis, hypothyroidism	MV involved 26 × 20-mm vegetation, presented with right-sided stroke	Brain emboli, immune phenomena, vascular phenomena	Underwent MVR; vancomycin planned for 6 wk, received 7 wk
52	M	BAV, congenital VSD, AR, TKA, ex-smoker	AV involved, "small" vegetation	None	No surgery; cefazolin planned for 6 wk; received 6 wk
62	M	DM, PVD, BPH, HTN, AF	No vegetation on echo, presented with sepsis	Osteomyelitis	No surgery; cefazolin planned for 6 wk; received 6 wk
63	M	MI, CABG, rapid AF with pre-excitation, HTN, dyslipidemia	MV involved, presented with CHF, 28 × 20-mm vegetation	Persistent bacteremia, vascular phenomena	Underwent MVR, modified De Vega TVR, PFO repair; cloxacillin planned for 6 wk, received 6 wk
66	M	HTN, cataracts, AF, anemia	No echo performed; treated per Duke's as possible IE, admitting diagnosis was multiple myeloma	Persistent bacteremia	No surgery; planned piptazo for 2 wk, received for 3 wk
89	M	AF, COPD, CKD, DM, HTN	AV involved, presented with sepsis, 15 × 3-mm vegetation	Persistent bacteremia, osteomyelitis	Not surgical candidate; cefazolin planned for 6 wk, received 6 wk

Outcome for all patients was discharge alive with clinical improvement, except for 1 (male, age 33 years) who died in the hospital.

AF, atrial fibrillation; AR, aortic regurgitation; AV, aortic valve; BAV, bicuspid aortic valve; BPH, benign prostatic hyperplasia; CABG, coronary artery bypass grafting; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; DLP, dyslipidemia; DM, diabetes mellitus; echo, echocardiography; F, female; HTN, hypertension; ICU, intensive care unit; IDU, injection drug use; IE, infective endocarditis; ILD, interstitial lung disease; M, male; MI, myocardial infarction; MS, multiple sclerosis; MV, mitral valve; MVR, MV replacement; PE, pulmonary embolism; PFO, PV, pulmonic valve; PVD, peripheral vascular disease; TKA, total knee arthroplasty; TV, tricuspid valve; TVR, tricuspid valve replacement; VSD, ventricular septal defect.

Table 2. Clinical characteristics of patients with *Staphylococcus lugdunensis* endocarditis

Characteristics	n/total = 8 (definite + possible per Duke's criteria)
Age, y, mean ± SD (range)	56.38 ± 17.56 (33–89)
Sex	
Male	6 (75)
Female	2 (25)
Portal of entry known	1 (12.5); 7 unknown (87.5)
Top 5 comorbidities (n of 8)	
1…	Hypertension (4)
2…	Atrial fibrillation (4)
3…	Diabetes mellitus (3)
4…	Pancreatitis (2)
5…	Anemia (1)
Injection drug use	1 (12.5)
Modified Duke criteria	
Possible	2 (25)
Definite	6 (75)
Requiring ICU	3 (37.5)
Location	
Left-sided	5 (62.5)
Mitral valve	3 (37.5)
Aortic valve	2 (25)
Right-sided	1 (12.5)
Tricuspid valve	1 (12.5)
Vegetations on echocardiography	6 (75)
Penicillin susceptible	6 yes (75), 1 non-susceptible (12.5%) and 1 not reported (12.5%)
Embolization	2 (25)
Surgery	2 (25)
Outcome	
Discharged alive	7 (87.5)
Death	1 (12.5)
Characteristics of valve	
Native valve	7 (87.5)
Prosthetic valve	1 (12.5)

Values are n (%), unless otherwise indicated.
ICU, intensive care unit; SD, standard deviation.

mainly over 50 years of age, with infection usually acquired in the community, and a portal of entry that often was not identified. Mostly left-sided valves (86.6%) were affected, with the mitral valve (40.3%) more commonly involved than the aortic valve (32.8%) and both mitral and aortic valve simultaneously (11.9%). Greater than 80% of infections were in native valves, 68.7% received valve replacement in addition to antibiotics, and patients with surgical interventions had better outcomes. Medical treatment alone corresponded to an odds ratio of 4.79 (1.16-19.78) for mortality. In our sample, average age, male predominance, and primarily left-sided valve infection were similar. Our *S. lugdunensis* isolates were also mostly penicillin- and oxacillin-sensitive. Conversely, we observed a lower rate of surgery and mortality. In addition, one of our patients had IDU, suggesting that it is a possible risk factor as it is with other coagulase-negative *Staphylococci*.[13] When *S. lugdunensis* has been implicated by percutaneous portal of entry, it has been related mainly to groin procedures, as perineal skin is an area where *S. lugdunensis* will preferentially reside.[18]

The rate of surgery and mortality in our sample were low, in contrast to previous findings.[2,19] Upon further review, other than having *S. lugdunensis* bacteremia, most of our medically managed patients did not meet standard surgical indications (see Table 5 in Baddour et al.).[13] Despite being offered medical management only, all of these patients appeared to have good outcomes at the time of discharge from the hospital. Alternatively, our patients with large vegetations, congestive heart failure, shock, and embolic phenomena—when deemed to be surgical candidates—did receive surgery, which also led to good outcomes. In other words, it *may be* possible to select patients for surgical interventions based on the traditional guideline-driven "clinical and echocardiographic features that suggest potential need for surgical intervention," rather than solely on the presence of *S. lugdunensis* endocarditis.[13] Our data suggest that a well selected patient with uncomplicated *S. lugdunensis* endocarditis may do well with medical therapy alone. However, we caution the reader that further studies—ideally prospective ones, including a larger number of patients in high-volume surgical centres—should be undertaken prior to drawing more-definitive conclusions.

The present study has noteworthy limitations, attributable to mainly the small sample size. As a consequence, we cannot make statistical comparisons with previous reviews.[2] That being said, we have contributed several cases to the literature that will serve well in a future systematic review. Furthermore, we are reporting on the experience at 2 centres only. Thus, our data should be interpreted with caution and should be used for hypothesis-generating rather than practice-changing. Finally, we do not have concrete data available on relapses and readmissions for discharged patients, but the absence of subsequent *S. lugdunensis* blood cultures in studied patients was used as a surrogate for such data.

Conclusion

S. lugdunensis is an uncommon but important cause of IE in the Saskatchewan population. Due to our overall small sample size, with a single patient known to have IDU, HIV and hepatitis C coinfectivity do not seem to be a significant epidemiologic factor. The principles of medical management of *S. lugdunensis* endocarditis cases should follow the standard of care for treatment of *Staphylococcal* endocarditis.[13] The need for surgical management may be guided more by traditional factors rather than the presence of *S. lugdunensis,* as empasized in the current literature. More cases with a focus on clinical outcomes should be reported to solidify confidence in this conclusion.

Acknowledgements

We thank Dr Joseph Blondeau and the Royal University Hospital Microbiology Laboratory personnel for their assistance in data gathering.

Funding Sources

The authors have no funding sources to declare.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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