Endocarditis due to Staphylococcus lugdunensis—a retrospective national registry–based study

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Abstract

We present characteristics of infective endocarditis (IE) caused by Staphylococcus lugdunensis and compare with IE caused by Staphylococcus aureus and other CoNS, in the National Swedish Registry of IE (2008–2018). Thirty episodes of S. lugdunensis IE were registered, of which 21 cases affected native valves, and 7 patients were subjected to surgery. The mortality rate at 30 days was significantly higher for S. lugdunensis IE (20%, n = 6), than for IE caused by other CoNS (7%) or S. aureus (9%) p = 0.016. Septic embolisation was only reported in two cases (7%). The most common treatment was isoxazolyl penicillin (n = 18).

Introduction

Staphylococcus lugdunensis belongs to the group of CoNS and was first described in 1988 [1–3]. Since then, S. lugdunensis has attracted increasing interest as a cause of infective endocarditis (IE). It is known to infect native valves to a larger extent than other CoNS, and to have a clinical presentation more similar to S. aureus [4]. Several case reports indicate that S. lugdunensis can cause severe IE with rapid destruction of heart valves and massive septic embolisation [5–9], and many studies have emphasised the importance of early surgical intervention [7, 8, 10]. S. lugdunensis is also often susceptible to narrow-spectrum antibiotics including penicillin, and recent reports have indicated that benzyl penicillin may be a better alternative for susceptible isolates than standard treatment with isoxazolyl penicillin or vancomycin [11–13].

Our aim was to describe the clinical presentation of IE caused by S. lugdunensis, and to compare it with the clinical presentation of IE caused by other CoNS and S. aureus. A secondary aim was to present the antibiotic treatment of S. lugdunensis IE.

Material and methods

We retrospectively reviewed cases of IE caused by S. lugdunensis, S. aureus and other CoNS from the Swedish Registry of Infective Endocarditis between 2008 and 2018.

Cases were classified according to Duke’s criteria [14, 15]. If information about comorbidities were missing, we interpreted it as a negation of that condition. For other missing data, no imputations were made. Treatment delay was defined as days from onset of symptoms until start of IE treatment. Definite antibiotic treatment was defined as the antibiotic given more than 50% of the treatment time. Antibiotic susceptibility data were received by personal contact with the local microbiological department at each site. Antibiotic susceptibility testing was performed according to EUCAST guidelines [16].

Comparisons between groups were made with chi-squared test when testing categorical variables and Mann-Whitney U test for continuous data. Survival data were calculated with a Kaplan-Meier survival curve and log-rank test. Two-tailed p < 0.05 was regarded as...
statistically significant. Analyses were performed using the
SPSS software, version 25 (SPSS, Armonk, NY, USA).
The study was approved by the Medical Ethics Committee
(Institutional Review Board) of Lund University (Dnr
2017/1002).

Results and discussion
In total, we found 30 cases of IE caused by S. lugdunensis, 262
cases of IE caused by other CoNS and 1892 cases of IE caused
by S. aureus. Clinical characteristics of the different groups are
summarised in Table 1. Patients with S. lugdunensis IE were
significantly older than patients with IE caused by S. aureus
(73 vs 66 years, \( p = 0.01 \)). When iv-drug users were excluded,
the median age of S. aureus cases increased to 69.5
years, and the age difference between the groups was no
longer significant (\( p = 0.44 \)). In agreement with previous
reports, 21 patients (70%) in the S. lugdunensis group had
native valve IE, and the most common localisation was the
aortic valve (60%) [7, 17]. The proportion of native valve
IE in the S. lugdunensis group was similar to that in
S. aureus IE, but significantly higher than for other CoNS
(70% vs 35%, \( p = 0.0001 \)).

Table 1  Patient characteristics and outcome data

| Bacteria (\( n \)) | S. lugdunensis \( n = 30 \) | CoNS \( n = 262 \) | \( P \) value CoNS vs S. lugdunensis | S. aureus \( n = 1892 \) | \( P \) value S. aureus vs S. lugdunensis |
|------------------|----------------------|-------------------|---------------------------------|----------------------|---------------------------------|
| **Background data** | | | | | |
| Age (years); median (IQR) | 73 (65–84) | 72 (61–80) | 66 (45–79) \( p = 0.01 \) | | |
| Gender-female | 11 (37%) | 86 (33%) | 725 (38%) | | |
| Diabetes | 9 (30%) | 58 (22%) | 349 (18%) | | |
| Cancer last 5 years | 6 (20%) | 46 (18%) | 173 (9%) \( p = 0.042 \) | | |
| IV drug users | 0 (0%) | 9 (3%) | 448 (24%) \( p = 0.002 \) | | |
| Prosthetic valve | 8 (27%) | 115 (44%) | 255 (14%) \( p = 0.037 \) | | |
| Pacemaker/ICD | 1 (3%) | 74 (28%) | 324 (17%) \( p = 0.046 \) | | |
| Native valve disease | 5 (17%) | 55 (21%) | 222 (12%) | | |
| Treatment delay, days median (IQR) | 9 (4–15) | 10 (3–26) | 5 (2–9) \( p < 0.001 \) | | |
| **Dukes criteria** | | | | | |
| Definite | 27 (90%) | 194 (74%) | 1544 (82%) | | |
| Possible | 3 (10%) | 67 (26%) | 338 (18%) | | |
| **Localisation** | | | | | |
| Aortic | 18 (60%) | 121 (46%) | 577 (31%) \( p = 0.001 \) | | |
| Mitral | 10 (33%) | 76 (29%) | 596 (32%) | | |
| Tricuspid | 1 (3%) | 22 (8%) | 441 (23%) \( p = 0.01 \) | | |
| **Type of infection** | | | | | |
| Prosthetic IE | 6 (20%) | 110 (42%) | 245 (13%) | | |
| Pacemaker/ICD IE | 1 (3%) | 48 (18%) | 179 (9%) | | |
| Native valve IE | 21 (70%) | 90 (35%) | 1103 (58%) | | |
| Community acquired | 25 (83%) | 179 (68%) | 1543 (82%) | | |
| **Outcome** | | | | | |
| Antibiotic treatment, median days (IQR) | 31 (18–37) | 35 (28–42) | 30 (28–40) | | |
| Embolisation | 2 (7%) | 62 (24%) | 907 (48%) \( p < 0.001 \) | | |
| Surgical intervention | 7 (23%) | 111 (42%) | 455 (24%) | | |
| Day of surgery, median (IQR) | 5 | 12 | 12 | | |
| (1–9) | (5–20) | | (7–23) | | |
| Mortality at 30 days | 6 (20%)* | 17 (7%) | 166 (9%) | | |
| In-hospital mortality | 7 (23%) | 49 (19%) | 268 (14%) | | |
| Day of death in hospital, Median (IQR) | 9 (8–23) | 36 (28–47) | 25 (14–39) \( p = 0.016 \) | | |

Data are presented as number and (%) unless otherwise stated. Survival data calculated with Kaplan-Meier survival curve and log-rank test.

ICD intracardiac device, IQR interquartile range

*\( p = 0.016 \)
There was a significantly lower occurrence of septic embolisation in patients with *S. lugdunensis* IE (7%, *n* = 2), both compared with the *S. aureus* group (48%, *p* < 0.001) and the other CoNS group (24%, *p* = 0.033). This is in contrast to earlier published studies, reporting a high frequency of severe septic embolisation [5, 6, 8, 9]. This discrepancy could be a result of previous publication bias, unthorough clinical examination or failure to report correctly to the database registry. Speaking against the latter is that the embolisation frequency for *S. aureus* was in line with previously published data [18].

Moreover, earlier studies have reported a need of surgical intervention in a large proportion of cases [5, 7, 19], but only seven patients with *S. lugdunensis* IE (23%) underwent surgery in our cohort. This was similar to the *S. aureus* group (24%) but lower than for other CoNS cases (42% vs 23%, *p* = 0.044), which can probably be attributed to the high proportion of prosthetic valve IE in the other CoNS group.

In-hospital mortality was comparable between the groups. However, death occurred after a median time of 9 days in the *S. lugdunensis* group, which was significantly earlier than both the groups of *S. aureus* (median 25 days, *p* = 0.016) and other CoNS (median 36 days, *p* = 0.007) as visualised in Fig. 1 and Table 1. This makes all-cause mortality at 30 days significantly higher in the *S. lugdunensis* group (20%, *n* = 6) compared with other CoNS (7%, *n* = 17) and *S. aureus* (9%, *n* = 166), *p* = 0.016. This indicates, as previously reported, that *S. lugdunensis* on some occasions can cause an aggressive form of IE, which supports the importance of early identification and early surgical intervention for this pathogen [7, 8, 10].

The most common antibiotic treatment of *S. lugdunensis* IE, given to 18 cases (60%), was an isoxazolyl penicillin. All isolates were reported susceptible to isoxazolyl penicillin, except for two isolates where data were missing. Despite this, 7 patients (23%) received treatment with different antibiotic combinations, and only one of these patients had a prosthetic valve IE. Only one isolate was tested for penicillin G even though *S. lugdunensis* is known to have a conserved susceptibility to most antibiotics [5, 12, 20]. Recent research has suggested penicillin to be the preferred treatment of *S. lugdunensis* infections [12], and reliable methods for susceptibility testing are available [21].

The most important weakness of this study is the small number of *S. lugdunensis* IE cases. Given the few cases of *S. lugdunensis* IE, this study was underpowered to detect any small differences between the groups, and statistically significant differences have to be interpreted with caution. Even so, this is to our knowledge the largest *S. lugdunensis* IE cohort described, and the registry-based design of the study adds important knowledge about the clinical presentation of *S. lugdunensis* IE.

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![Kaplan-Meier plot survival after hospitalisation with IE caused by different staphylococci](image)
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