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Clinical presentation of infective endocarditis caused by different groups non-beta haemolytic streptococci

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Running title: Infective endocarditis caused by streptococci

Abstract

Purpose: Streptococci are common causes of infective endocarditis (IE) and matrix-assisted laser desorption ionization - time of flight mass spectrometry (MALDI-TOF MS) has provided a practical tool for their species determination. We aimed to investigate if particular groups of non-beta heamolytic streptococci were associated to IE or to specific presentations thereof.

Methods: The Swedish registry for infective endocarditis was used to identify cases of IE caused by streptococci and a local database to identify cases of streptococcal bacteremia. The bacteria were grouped using MALDI-TOF MS and the clinical characteristics of IE caused by different groups were compared.

Results: We determined the group of 201 streptococcal IE isolates; 18 isolates belonged to the anginosus, 19 to the bovis, 140 to the mitis, 17 to the mutans, and 7 to the salivarius groups. The mitis and mutans groups were significantly more common and the anginosus group less common among IE cases as compared to all cause bacteremia. Patients infected with bovis group isolates were older, had more cardiac devices, and had more commonly prosthetic valve IE compared to IE caused by streptococci of the other groups. Twenty-one percent of patients needed surgery and in hospital mortality was eight percent with no significant differences between the groups.

Conclusions: Grouping of non-beta haemolytic streptococci using MALDI-TOF MS can provide a basis for decision-making in streptococcal bacteremia. IE caused by bovis group isolates have clinical characteristics distinguishing them from IE caused by other groups of *Streptococcus*.

Keywords: Streptococcus, infective endocarditis, prognosis, MALDI-TOF MS, *Streptococcus mitis*, *Streptococcus bovis*.

Introduction

Infective endocarditis (IE) is a severe infection where non beta-haemolytic streptococci are common causative agents [1,2]. Streptococci isolated in IE most often belong to the viridans or the bovis group [1]. The viridans streptococci are genetically diverse and are divided into the anginosus, mitis, mutans, and salivarius groups [3]. Within each group, there are several species and subspecies. Biochemical methods are unreliable in species determination of streptococci [4] whereas genetic methods, such as sequencing of one or more genes, is more reliable but is yet not practical for use in the routine laboratory [3]. Matrix-assisted laser desorption ionization - time of flight mass spectrometry (MALDI-TOF MS) has recently been introduced in many laboratories and has been found useful in species determination of viridans and bovis streptococci [5-7].

Several studies have investigated the distribution of streptococcal species in IE but the results are difficult to compare due to the different methods for species determination used. In a majority of reports, the most common cause of streptococcal IE are mitis group isolates [8-11] whereas bovis group isolates are reported in a variable proportion ranging from a few per cent to almost half of isolates [9,11,12]. Isolates from the mutans group are less frequently encountered but seem to be more common in IE than in all-cause bacteremia [8,13] whereas isolates from the anginosus group is less frequently encountered in IE than in all-cause bacteremia [4,8]. Isolates of the salivarius group are rarely encountered [8,9]. Patients with IE caused by bovis group isolates have been reported to be older and to have more co-morbidities than patients with IE caused by other streptococci [8,9,14]. An association between IE with bovis

group isolates and colorectal neoplasia has also been established [15]. It is at present not clear if other differences between underlying factors or clinical presentation of IE caused by different streptococcal groups exist.

The Swedish Registry of Infective Endocarditis (SRIE) receives voluntary reports from all thirty departments of infectious diseases in Sweden. During the 20-year period, 1995 – 2014, 6775 adult episodes have been registered which has been estimated to cover approximately 75% of all episodes in Sweden [16]. We have previously used the SRIE to describe the features of aerococcal IE [17] and here we employ the SRIE to identify cases of IE with streptococci. We group the bacteria using MALDI-TOF MS and compare clinical features of IE caused by different streptococcal groups.

Materials and methods

The SRIE was searched for cases of IE caused by "alpha streptococci" or "*Streptococcus bovis"* reported between 2008 and 2014. Episodes had been reported on a standardized internet-based questionnaire. The relevant laboratories of clinical microbiology were contacted and stored streptococcal isolates were collected for reanalysis in our laboratory with MALDI-TOF MS as described in [18]. Alternatively, for laboratories employing MALDI-TOF MS as primary species determination method, the result was obtained from that laboratory. To allow secure identification bacteria were grouped into five groups; *Streptococcus anginosus* group, *Streptococcus bovis* group, *Streptococcus mitis* group, *Streptococcus mutans* group, and the *Streptococcus salivarius* group. Score values above 2.0 were required for group determination.

The Laboratory Information System database of the laboratory for Clinical Microbiology in Skåne was searched for blood cultures positive for viridans and bovis streptococci of above groups and their respective species between 2012 and 2014. This laboratory is the only one in a defined geographic area with 1.2 million inhabitants and employs MALDI-TOF MS as primary species determination method with a cut-off score of 2.0.

Differences were tested for statistical significance with Chi^2 test or the Wilcoxon rank number test using GraphPad Prism version 6. The local Ethics Committee approved of this study (reference number 2013/182).

Results

774 episodes of IE caused by alpha-streptococci or bovis streptococci were identified from SRIE. From these episodes, 116 isolates were obtained from laboratories that still had the bacteria in store and analysed with MALDI-TOF MS. The species determination and antibiotic susceptibility for 45 of these isolates have been described previously [19]. Data on streptococcal group for an additional 85 isolates was obtained from the respective laboratory. Of the 201 isolates, 18 isolates belonged to the anginosus group, 19 to the bovis group, 140 to the mitis group, 17 to the mutans group, and 7 to the salivarius group. The distribution of groups within the IE patients was compared to the group distribution of all cause bacteremia with the same streptococcal groups (n=850) (Figure 1). Isolates of the mutans and mitis groups were more common among IE patients whereas isolates of the anginosus group were less common in IE ($p<0.001$ for a difference using the Chi^2 test).

Information from the SRIE on the cases of IE caused by streptococci of different groups is summarized in table 1. The patients were predominantly male and the median age was 59-78 with significantly younger patients in the mitis and mutans groups. 76 % of all episodes were classified as definite cases with non-significant differences between the groups. A significantly higher proportion of patients with IE caused by the bovis group had pacemaker or ICD and prosthetic valve IE was more common among patients with bovis group isolates. Embolization was seen in 25 % (50 patients), most commonly to the brain (20 patients) or bone tissue (17 patients). In 21 % of patients surgery was performed, most commonly due to progressive heart failure (21 out of 42 patients) or large vegetations (17 out of 42 patients). Mortality during hospital admission was 8 % with no significant differences between the non-hemolytic streptococcal groups.

Discussion

Streptococci have been difficult to speciate but with the introduction of MALDI-TOF MS, a clinically useful tool for species determination has been provided [5-7]. This study demonstrates that mutans and mitis group isolates, as identified by MALDI-TOF MS, are overrepresented in patients with IE whereas the anginosus group is more common in all cause bacteremia than in IE. This finding is in line with previous studies [8] and underline the fact that different streptococci have different propensities to cause IE. This can be related to that mitis and mutans groups are members of the mouth flora rather than the intestinal flora, but differences in molecular virulence mechanisms such as propensity to aggregate human platelets may also play a role [20]. The

association of certain streptococcal groups with IE may help clinicians to determine which patients with streptococcal bacteremia that should be referred to transesophageal echocardiography to detect IE.

The low number of bovis group isolates in our material is in contrast to findings from other European countries such as France [12] and Germany [11] where such isolates are common causes of IE. Moreover, in the US, a large increase in the incidence of bovis group IE was noted between the 1940ies and the 1970ties [9]. The reasons for the large geographical and temporal differences in incidence of IE caused by the bovis group are unknown but is not likely to be due to methodological problems only, since authors utilizing identical protocols for species determination have reported very different figures in different populations [9,11].

The present study is the largest one where a validated species determination of streptococci and a relatively detailed description of IE cases are available. However, the statistical power of the study to detect differences in the clinical presentations between the groups was hampered by the low number of isolates in the anginosus, bovis, mutans, and salivarius groups. The main findings from the comparative part of the study were that the patients infected with bovis group isolates tended to be older, have more cardiac devices, have a more acute onset of disease, and in a larger proportion have prosthetic valve IE. These findings are partly in line with previous reports of bovis isolates infecting older persons with more comorbidities and less pre-existing native valve disease [14].

The increased propensity of bovis to cause prosthetic valve IE has not been reported previously.

In this study we chose to divide the streptococci into groups rather than into species, since this allow secure and correct identification using MALDI-TOF MS. The advantage of our approach is that the risk for misclassification of the bacteria is lower at group level than at species level and that the material, despite being relatively large, would loose power from a stratification into species. The risk of our approach, however, is that relevant differences between certain species will not be detected. Further studies, comparing the presentation of IE with selected common streptococcal species, are needed as are studies to determine the risk for a certain individual with streptococcal bacteremia to have IE.

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Legend for figure

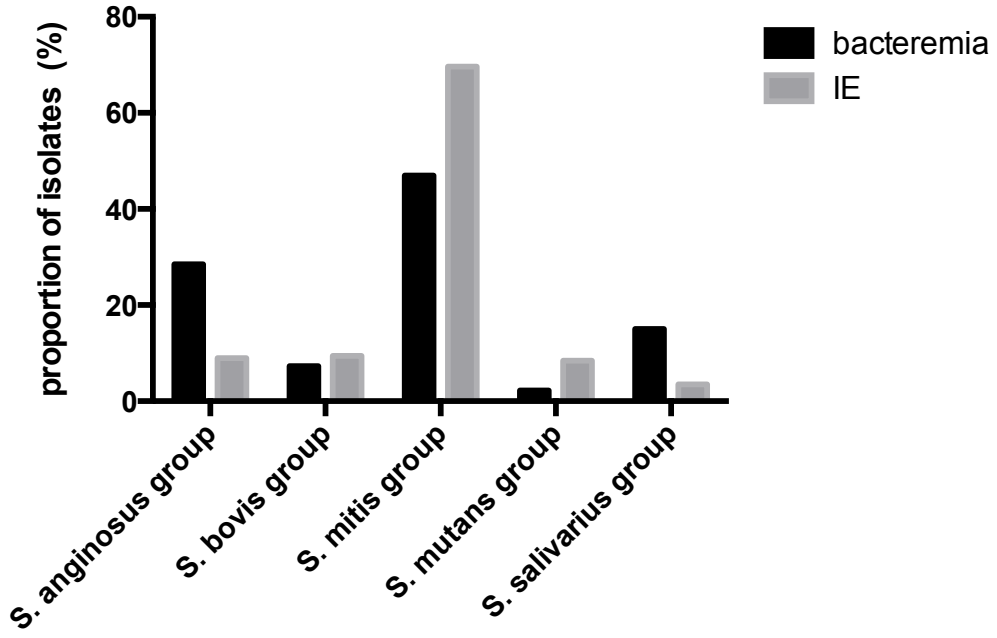
Figure 1. The proportions of the different streptococcal groups indicated among all bacteremia isolates (n=850, black bars) and of IE isolates (n=201, grey bars) are given.

Table 1. Comparison of IE caused by different non-beta haemolytical streptococcal groups

	S. anginosus group	*S. bovis* group	*S. mitis* group	*S. mutans* group	*S. salivarius* group	All groups
	n=18	n=19	n=140	n=17	n=7	n=201
Age, (years, median)**	78	75	65	59	78	67
Gender (% male)	78	58	68	76	57	68
Underlying disease						
Diabetes (%)	25	36	17	10	50	20
Cancer (%)	10	11	16	11	33	15
IVDU[1] (%)	6	0	4	6	0	3
Underlying heart disease						
Native valve disease (%)	22	16	39	24	43	34
Prosthetic heart valve (%)	11	37	19	18	0	19
Previous IE (%)	6	16	9	12	0	9
Pacemaker/ICD (%) *	17	42	12	0	33	15
Type of infection						
NVE, left, isolated (%)	44	47	69	65	71	64
NVE, right (%)	6	5	4	12	0	5
PVE (%)*	11	37	14	18	0	18
PME (%)	6	5	1	0	0	2
Aortic valve (%)	33	63	43	47	43	44
Mitral valve (%)	39	26	40	35	29	38
Nosocomial (%)	11	0	4	0	14	4
Course of disease						
Onset to treatment (days)	16	8	16	21	12	16
Hospital duration (days)	27	30	28	22	37	28
Treatment duration (days)	24	30	28	26	24	28
Treatment duration AG (days)	14	14	14	14	14	14
Embolization (%)	33	21	26	24	14	26
Surgery during treatment (%)	17	26	20	35	14	21
In-hospital death (%)	6	11	7	6	29	8

[1]Abbreviations used are; IVDU; intravenous drug use, ICD; intracardiac device, NVE; native valve endocarditis, PVE; prosthetic valve endocarditis, PME; pacemaker endocarditis, AG; aminoglycoside. * indicates $p<0.05$, ** indicates that $p<0.01$.

Figure 1


proportion of isolates (%)
80
60
40
20
0
bacteremia
IE
S. anginosus group
S. bovis group
S. mitis group
S. mutans group
S. salivarius group