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1 Clinical presentation of infective endocarditis
2 caused by different groups non-beta haemolytic
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4
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22

23 **Running title:** Infective endocarditis caused by streptococci

24 **Abstract**

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

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

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

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

47

48 **Keywords:** Streptococcus, infective endocarditis, prognosis, MALDI-TOF MS,

49 *Streptococcus mitis*, *Streptococcus bovis*.

50

51 **Introduction**

52 Infective endocarditis (IE) is a severe infection where non beta-haemolytic
53 streptococci are common causative agents [1,2]. Streptococci isolated in IE
54 most often belong to the viridans or the bovis group [1]. The viridans
55 streptococci are genetically diverse and are divided into the anginosus, mitis,
56 mutans, and salivarius groups [3]. Within each group, there are several species
57 and subspecies. Biochemical methods are unreliable in species determination of
58 streptococci [4] whereas genetic methods, such as sequencing of one or more
59 genes, is more reliable but is yet not practical for use in the routine laboratory
60 [3]. Matrix-assisted laser desorption ionization - time of flight mass
61 spectrometry (MALDI-TOF MS) has recently been introduced in many
62 laboratories and has been found useful in species determination of viridans and
63 bovis streptococci [5-7].

64 Several studies have investigated the distribution of streptococcal species in IE
65 but the results are difficult to compare due to the different methods for species
66 determination used. In a majority of reports, the most common cause of
67 streptococcal IE are mitis group isolates [8-11] whereas bovis group isolates are
68 reported in a variable proportion ranging from a few per cent to almost half of
69 isolates [9,11,12]. Isolates from the mutans group are less frequently
70 encountered but seem to be more common in IE than in all-cause bacteremia
71 [8,13] whereas isolates from the anginosus group is less frequently encountered
72 in IE than in all-cause bacteremia [4,8]. Isolates of the salivarius group are
73 rarely encountered [8,9]. Patients with IE caused by bovis group isolates have
74 been reported to be older and to have more co-morbidities than patients with IE
75 caused by other streptococci [8,9,14]. An association between IE with bovis

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

79

80 The Swedish Registry of Infective Endocarditis (SRIE) receives voluntary
81 reports from all thirty departments of infectious diseases in Sweden. During the
82 20-year period, 1995 – 2014, 6775 adult episodes have been registered which
83 has been estimated to cover approximately 75% of all episodes in Sweden [16].

84 We have previously used the SRIE to describe the features of aerococcal IE
85 [17] and here we employ the SRIE to identify cases of IE with streptococci. We
86 group the bacteria using MALDI-TOF MS and compare clinical features of IE
87 caused by different streptococcal groups.

88

89 **Materials and methods**

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

101 The Laboratory Information System database of the laboratory for Clinical
102 Microbiology in Skåne was searched for blood cultures positive for viridans
103 and bovis streptococci of above groups and their respective species between
104 2012 and 2014. This laboratory is the only one in a defined geographic area
105 with 1.2 million inhabitants and employs MALDI-TOF MS as primary species
106 determination method with a cut-off score of 2.0.

107 Differences were tested for statistical significance with Chi² test or the
108 Wilcoxon rank number test using GraphPad Prism version 6. The local Ethics
109 Committee approved of this study (reference number 2013/182).

110

111 **Results**

112 774 episodes of IE caused by alpha-streptococci or bovis streptococci were
113 identified from SRIE. From these episodes, 116 isolates were obtained from
114 laboratories that still had the bacteria in store and analysed with MALDI-TOF
115 MS. The species determination and antibiotic susceptibility for 45 of these
116 isolates have been described previously [19]. Data on streptococcal group for
117 an additional 85 isolates was obtained from the respective laboratory. Of the
118 201 isolates, 18 isolates belonged to the anginosus group, 19 to the bovis group,
119 140 to the mitis group, 17 to the mutans group, and 7 to the salivarius group.
120 The distribution of groups within the IE patients was compared to the group
121 distribution of all cause bacteremia with the same streptococcal groups (n=850)
122 (Figure 1). Isolates of the mutans and mitis groups were more common among
123 IE patients whereas isolates of the anginosus group were less common in IE
124 (p<0.001 for a difference using the Chi² test).

125

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

139

140 **Discussion**

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

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

154

155 The low number of bovis group isolates in our material is in contrast to findings
156 from other European countries such as France [12] and Germany [11] where
157 such isolates are common causes of IE. Moreover, in the US, a large increase in
158 the incidence of bovis group IE was noted between the 1940ies and the
159 1970ties [9]. The reasons for the large geographical and temporal differences in
160 incidence of IE caused by the bovis group are unknown but is not likely to be
161 due to methodological problems only, since authors utilizing identical protocols
162 for species determination have reported very different figures in different
163 populations [9,11].

164

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

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

177

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

188

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196

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270

271

272

273

274 **Legend for figure**

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

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

	<i>S. anginosus</i>	<i>S. bovis</i>	<i>S. mitis</i>	<i>S. mutans</i>	<i>S. salivarius</i>	All
	group	group	group	group	group	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

¹Abbreviations 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

