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1 RESEARCH NOTE

2 **Characteristics and prognosis of pneumococcal endocarditis: a**
3 **case-control study**4 **Running title:** Pneumococcal endocarditis

5

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23 Case series have suggested that pneumococcal endocarditis is a rare disease, mostly reported
24 in patients with comorbidities but no underlying valve disease, with a rapid progression to
25 heart failure, and high mortality. We performed a case-control study of 28 patients with
26 pneumococcal endocarditis (cases), and 56 patients with non-pneumococcal endocarditis
27 (controls), not matched on sex and age, during years 1991-2013, in one referral center.
28 Alcoholism (39.3% vs. 10.7%; $P < .01$), smoking (60.7% vs. 21.4%; $P < .01$), the absence of
29 previously known valve disease (82.1% vs. 60.7%; $P = 0.047$), heart failure (64.3% vs. 23.2%;
30 $P < .01$), and shock (53.6% vs. 23.2%; $P < .01$) were more common in pneumococcal than in
31 non-pneumococcal endocarditis. Cardiac surgery was required in 64.3% of patients with
32 pneumococcal endocarditis, much earlier than in patients with non-pneumococcal
33 endocarditis (mean time from symptoms onset, 14.1 ± 18.2 vs. 69.0 ± 61.1 days). In-hospital
34 mortality rates were similar (7.1% vs. 12.5%). *Streptococcus pneumoniae* causes rapidly
35 progressive endocarditis requiring life-saving early cardiac surgery in most cases.

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37 **Keywords:** Endocarditis; *Streptococcus pneumoniae*; Heart failure; Cardiac surgery; Case-
38 control study

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42 Infective endocarditis (IE) is a severe disease with in-hospital and 5 year-mortality rates at
43 20%, and 40%. *Staphylococcus aureus* is the leading cause of IE [1, 2], and one of the most
44 virulent [3]. *Streptococcus pneumoniae*, responsible for <1% of IE [2], has also been
45 associated with rapidly progressive IE, extensive valvular destruction, heart failure, and high
46 lethality, in case reports or series published >10 years ago [4-6], but no comparative study has
47 been performed between pneumococcal endocarditis (PE) and endocarditis related to other
48 pathogens. We aimed to characterize the clinical features, and prognosis of pneumococcal
49 endocarditis (PE), as compared to IE caused by other bacteria.

50 We performed an observational study of all patients admitted with PE at the Rennes
51 University Hospital, a 1500-bed tertiary care teaching hospital that serves as the referral
52 center for IE in western France, during years 1991-2013. Patients with suspected IE were
53 managed by a multidisciplinary 'endocarditis team', as recommended [7, 8]. Cases were
54 identified through computerized database. Only patients with definite IE, according to the
55 modified Duke criteria [9], were enrolled. Data were extracted from medical charts through a
56 standardized questionnaire. Euroscore I and II were calculated for each patient who
57 underwent cardiac surgery during the acute phase of IE [10]. Follow-up data were collected
58 by phone calls to primary physicians, patients, or through the civil registry.

59 A case-control study was performed to compare PE with IE due to other bacteria. Two
60 controls were selected for each case: the patients with non-pneumococcal IE who were
61 admitted just before, and just after, each case of PE. The cases and controls were not matched
62 on age and sex. Continuous variables were expressed as mean \pm standard deviation (SD), and
63 categorical variables as numbers (%). PE and non-pneumococcal IE were compared using
64 Chi-square test or Fisher's exact test, as appropriate. A $P < .05$ was considered statistically
65 significant. Survival analyses were performed using the Kaplan-Meier method. For all

66 statistical analyses, SAS software 9.3 was used, except for survival analyses, performed by
67 SPSS software.

68 We enrolled 28 patients with definite PE (cases), and 56 patients with non-
69 pneumococcal definite IE (controls), including IE related to *Staphylococcus aureus* (n=21),
70 non-pneumococcal *Streptococcus* spp (n=20), *Enterococcus* spp (n=8), other gram-positive
71 cocci (n=4), and gram-negative bacilli (n=3). Patients with PE had a mean age of 59.1 ± 15.3
72 years at diagnosis, were mostly male (n=19, 67.8%), smokers (n=17, 60.7%), with no
73 previously known valve disease (n=20, 71.4%). They presented with fever (n=28, 100%), and
74 heart murmur (n=19, 67.8%). Infection source was pneumonia (n=12, 42.8%), or unknown
75 (n=11, 39.2%). Eight patients (28.6%) had meningitis, of whom 3 presented with the Austrian
76 syndrome (PE, meningitis, and pneumonia). Echocardiographic examination found
77 vegetations in 88.4% of patients (mean size, 18.7 ± 6.8 mm). Mean left ventricular ejection
78 fraction was 57.4% (range, 45-70). Two patients had pericarditis. All *S. pneumoniae* strain
79 were susceptible to penicillin, with minimal inhibitory concentration (MICs) <0.5 mg/L,
80 except one with MIC=1.0 mg/L. All patients were treated with high-dose intravenous
81 penicillin, for a mean duration of 37.9 ± 20.3 days, in association with gentamicin during the
82 first 14 days for 19 patients (67.8%). Among these 19 patients, two developed acute renal
83 failure requiring gentamicin discontinuation. Main complications were heart failure (n=18,
84 64.2%), shock (n=15, 53.6%), and stroke (n=5, 17.8%)

85 Eighteen patients (64.3%) underwent cardiac surgery. Their mean Euroscore I and II
86 were, respectively, $30.1 \pm 20.0\%$, and $18.8 \pm 16.9\%$. Per-operative findings included
87 vegetations (n=16), perivalvular abscess (n=13), and intracardiac fistula (n=5). Cardiac
88 surgery included valvular replacement (n=17: 9 bioprosthesis and 8 mechanical valve),
89 valvuloplasty (n=3), and repair of intracardiac defect with pericardial patch or surgical felt
90 (n=13). Three patients required additional cardiac surgery, including two who underwent

91 heart transplant [11]. The 30-day post-operative survival rate was 100%. Mean duration of
92 hospitalization was 48.0 ± 29.2 days. At last contact, 13 patients (46.4%) had died, of cancer
93 (n=4), heart failure (n=3), alcohol-related end-stage liver disease (n=2), or unknown cause
94 (n=4). In-hospital, and 5-year mortality rates were, respectively, 7.1% and 54.1% (figure 1).
95 As compared to non-pneumococcal endocarditis, PE were more common in patients without
96 previously known valvular disease, chronic alcohol intoxication, and smokers. Meningitis,
97 heart failure and shock were more likely to occur during the course of PE, than non-
98 pneumococcal IE. Patients with PE required cardiac surgery earlier than patients with non-
99 pneumococcal IE (table I). In-hospital and 1-year mortality were not different between
100 patients with PE, and non-pneumococcal IE, although there was a trend towards higher 5-year
101 mortality in the PE group.

102 Although few series have suggested that PE mostly occur in patients with
103 comorbidities (especially alcoholism), no previously known valve disease [6, 12], and rapidly
104 progress to heart failure, no comparative study have been reported to date. This case-control
105 study confirms previous findings [4, 5], and adds information in the field. Firstly, alcoholism
106 and smoking are more common in patients with PE, than in patients with non-pneumococcal
107 endocarditis, which may be related to the specific impact of these comorbidities on immunity
108 against invasive pneumococcal diseases [12-14]. Secondly, PE more commonly occurs in
109 patients with no previously known valve disease, which may be related to a combination of i)
110 specific virulence factors harboured by *S. pneumoniae*, that may lead to endocarditis in the
111 absence of pre-existing valvular lesions; ii) high prevalence of undiagnosed valve lesions in
112 patients with alcoholism and smoking, due to limited medical follow-up. Thirdly, the rapid
113 progression of PE is documented in this study, as previously [4][5], heart failure and shock
114 being encountered in >50% of patients. Lastly, despite these unfavourable prognostic factors,
115 the early outcome was good in all patients who benefited from cardiac surgery during the

116 acute phase of IE, with a mean delay from symptoms onset to surgery of 14.1 ± 18.2 days in
117 patients with PE, as compared to 69.0 ± 61.1 days in patients with non-pneumococcal IE
118 ($P < 0.001$). Of note, in-hospital mortality was $< 10\%$ despite mean Euroscore I, and II were,
119 respectively, 30.1% and 18.8%, but more than half of patients died within the 5 years
120 following diagnosis of PE, deaths being more frequently related to comorbidities.

121 Our study has limitations. This was a single-center observational study, over 23 years,
122 which may introduce biases, hence our findings may not be applicable to all settings. Cases
123 and controls were voluntarily not matched on sex and age, which allowed us to study the
124 impact of these variables. However, this is the first comparative study of pneumococcal
125 versus non-pneumococcal IE, which allows the identification of significant features that
126 differentiate PE from non-pneumococcal IE: PE more commonly occur in patients with
127 comorbidities (alcoholism, smoking), no underlying valve disease, with a rapid progression to
128 heart failure. This study advocates for early surgery for all patients with criteria for cardiac
129 surgery, as endocarditis-related mortality is low in patients who benefited from early surgery.

130

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133

134 **Transparency declaration**

135 All authors: none

136

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188 pneumococcal infections. *International journal of infectious diseases : IJID : official*
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1 **TABLE I.** Comparison of pneumococcal endocarditis (cases), and non-pneumococcal
 2 infective endocarditis (controls*)

Characteristics	Pneumococcal endocarditis (n=28)	Endocarditis due to other bacteria (n=56)	P value
Baseline			
Age, years (mean \pm SD)	59.1 \pm 15.3	60.9 \pm 15.3	NS
Male gender, n (%)	19 (67.8)	40 (71.4)	NS
Alcoholism, n (%)	11 (39.3)	6 (10.7)	< 0.01
Smoking, n (%)	17 (60.7)	12 (21.4)	< 0.01
Previously known valvular disease	5 (17.9)	22 (39.3)	0.047
Valve(s) involved, n (%)			
Aortic	19 (70.4)	35 (62.5)	NS
Mitral	10 (37.0)	28 (50.0)	NS
Tricuspid	3 (11.1)	2 (3.6)	NS
Pulmonary	1 (3.7)	0 (0)	NS
Two or more valves	4 (14.8)	9 (16.1)	NS
Peri-valvular abscess	8 (34.8)	17 (30.4)	NS
Cardiac surgery, n (%)			
Cardiac surgery, n (%)	18 (64.3)	31 (55.4)	NS
Time from symptoms onset to surgery (days \pm SD)	14.1 \pm 18.2	69.0 \pm 61.1	< 0.001
Time from admission to surgery (days \pm SD)	13.3 \pm 17.1	34.3 \pm 43.0	0.02
Complications			
Shock, n (%)	15 (53.6)	13 (23.2)	< 0.01
Heart failure, n (%) [‡]	18 (64.3)	13 (23.2)	< 0.01
Embolism, n (%)	5 (17.9)	16 (28.6)	NS
Meningitis, n (%)	8 (28.6)	3 (5.4)	< 0.01
In-hospital mortality, n (%)	2 (7.1)	7 (12.5)	NS
5-year mortality, n (%)	11 (39.3)	10 (17.9)	NS

3 SD, standard deviation ; NS, not significant

4 ‡ Heart failure was defined as patients with New-York Heart Association (NYHA)
5 class III or IV, and a chest radiograph compatible with heart failure

6 * Controls were endocarditis due to *Staphylococcus aureus* (n=21), non-pneumococcal
7 *Streptococcus* spp (n=20), *Enterococcus* spp (n=8), other gram-positive cocci (n=4), and
8 gram-negative bacilli (n=3).

ACCEPTED MANUSCRIPT

1 **FIGURE I.** Kaplan-Meier curve for cumulative survival probability

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