Characteristics and prognosis of pneumococcal endocarditis: a case-control study

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RESEARCH NOTE

Characteristics and prognosis of pneumococcal endocarditis: a case-control study

Running title: Pneumococcal endocarditis

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

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

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

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

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

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

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

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

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

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

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

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

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TABLE I. Comparison of pneumococcal endocarditis (cases), and non-pneumococcal infective endocarditis (controls*)

Characteristics	Pneumococcal endocarditis (n=28)	Endocarditis due to other bacteria (n=56)	P value
Baseline			
Age, years (mean ± SD)	59.1 ± 15.3	60.9 ± 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 (%)	18 (64.3)	31 (55.4)	NS
Time from symptoms onset to surgery (days ± SD)	14.1 ± 18.2	69.0 ± 61.1	< 0.001
Time from admission to surgery (days ± SD)	13.3 ± 17.1	34.3 ± 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

SD, standard deviation ; NS, not significant

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

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

FIGURE I. Kaplan-Meier curve for cumulative survival probability