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Short Communication

Be careful about MICs to amoxicillin for patients with *Streptococci*-related infective endocarditis

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ABSTRACT

Background: A variety of microorganisms can cause infective endocarditis (IE), with *Staphylococci* and *Streptococci* accounting for the majority of cases. *Streptococci* are a common cause of community-acquired IE but few studies have focused on this subgroup of endocarditis.
Methods: A retrospective multicentre study was conducted between 2012 and 2017 in 12 hospital centres in France. Data were extracted from the local diagnosis-related group database and matched with microbiological results. After identification, the records were retrospectively analysed.
Results: A total of 414 patients with streptococcal endocarditis were included. The patients were predominantly male (72.8%) and the median age was 73.2 years (interquartile range [IQR] 61.3-80.9). The majority of patients (70.6%) had native valve endocarditis. Embolic complications were seen in 38.8% of patients. Viridans group *Streptococci* (VGS) and *bovis-equinus* group *Streptococci* (BGS) accounted for 52.4% and 34.5% of isolated strains, respectively. Minimum inhibitory concentrations (MICs) of amoxicillin were <0.125, 0.125-2 and >2 mg/L for 59.6%, 27% and 1% of isolates, respectively. In-hospital mortality for patients with *Streptococci*-related IE was 17.8%. In multivariate analysis, the only factor associated with in-hospital mortality was MIC for amoxicillin between 0.25 and 2 mg/L ($P = 0.04$; OR = 2.23 [95% confidence interval (CI) 1.03-4.88]) whereas performance of cardiac surgery for IE was a protective factor ($P = 0.001$, OR = 0.23 [95% CI 0.1-0.56]).
Conclusions: IE remains a serious and deadly disease despite recent advances in diagnosis and treatment. Adaptation of antibiotic doses to MICs for amoxicillin and surgery may improve patient outcome.

1. Introduction

Infective endocarditis (IE) is associated with high rates of morbidity and mortality [1,2]. Despite advances in diagnosis, medical therapy and surgical treatment, in-hospital mortality rate for patients with IE is up to 20%, with a one-year mortality ranging from 25% to 40% [3]. Streptococci are the causative organisms in 30-40% of cases of IE [4] and remain the most common pathogens

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among patients in low-income countries, where predisposing heart disease as rheumatic carditis is widespread. Streptococci are normal inhabitants of the oral cavity and the gastrointestinal tract. In France, the rate of IE caused by *Streptococcus bovis* is notably higher than in many other countries [2]. This retrospective multicentre study focuses on a large cohort of patients with streptococci-related IE with particular emphasis on microbial aetiologies, antibiotic susceptibility testing results and clinical outcomes.

2. Materials and Methods

2.1. Study design

This observational retrospective study included all consecutive cases of IE related to *Streptococcus* spp. from 12 French hospitals between 2012 and 2017.

2.2. Patient selection

All patients aged at least 18 years with IE that matched Duke criteria [5] were included in the analysis. Data were extracted from the local diagnosis-related group database and matched with microbiological results. Prosthetic valve endocarditis was considered early-onset if it occurred within the first year after valve implantation and late-onset if it occurred thereafter. The specific variables included and analysed in the study were date of IE diagnosis, patient age and sex, co-morbidities, clinical presentation, type of IE (native or prosthetic), causative bacteria, type of complication (embolism, renal insufficiency, valve replacement), date of the start of antimicrobial treatment, date of surgery (if performed), and clinical outcome.

2.3. Microbiological diagnosis

Blood cultures (BC) were collected systematically from each patient with suspected IE. Gram staining and standard culture conditions were performed for all positive BC according to local guidelines. Positive BC were plated on blood agar plates (under aerobic and anaerobic conditions) and on Polyvitex chocolate agar plates (under 5% CO_2) at 35°C.

Identification of streptococci isolates at the species level was performed using matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF/MS). The dissection within the *bovis-equinus* group *Streptococci* was performed according to the analysis of the French National Reference Center for *Streptococci* (NRC) [6].

Antimicrobial susceptibility testing could be performed using the disk diffusion method according to the CA-SFM/EUCAST guidelines. MICs of amoxicillin were determined by Etest (bioMérieux) strips in accordance with the manufacturer's recommendations.

2.4. Definitions

The start of antimicrobial therapy was established as the first day of appropriate antibiotic therapy according to antimicrobial results.

The indication of cardiac surgery was determined according to accepted guidelines [5] and the final decision was made in agreement with cardiologists and cardiac surgeons. The time to surgery was the interval between the diagnosis of IE and the date of surgery.

Table 1
Demographic and clinical characteristics of 414 patients with *Streptococci*-related infective endocarditis.

Characteristic	N (%)
Demographic characteristic	
Males	302 (72.8)
Median age (y) [range]	73.2 [61.3 – 80.9]
Clinical characteristic	
Modified Duke Classification	
Definite	322 (78)
Possible	92 (22)
Valve type	
Native	293 (70.6)
Prosthetic	107 (25.7)
Device-related IE	14 (3.4)
*Valve involved**	
Aortic	240 (60)
Mitral	167 (40.3)
Tricuspid	17 (4.1)
Pulmonary	2 (0.5)
ICED	16 (3.9)
Amoxicillin MIC results	
≤0.125 mg/L	247 (59.6)
0.25-2 mg/L	112 (27)
>2 mg/L	3 (1)
NA	52 (12.6)
Presumed source of infection	
Non-oral gastrointestinal tract	92 (22.3)
Oral	126 (30.4)
Other	28 (6.7)
Unknown	168 (40.6)
Treatment	
Antibiotic therapy	414 (100)
Surgical treatment	155 (37.4)
In-hospital mortality	74 (17.8)

* Some patients presented infective endocarditis with multiple valvular involvementsICED: intra-cardiac electronic device, MIC: minimum inhibitory concentration, NA: Not available

2.5. Statistical analysis

The relationship between unfavourable outcome, defined as in-hospital mortality, and potential predictors was investigated using multivariable logistic analysis.

Results were expressed as the median (range) for continuous variables and N (%) for categorical variables. Variables showing associations at a significance level of α=0·20 in a univariable analysis were selected for inclusion in the multivariable model and a stepwise selection was done. Statistical analysis was done with R software (version 3.2.2). All tests were two-tailed and *P*-values less than 0.05 (calculated by χ. test, Student's t test, or Mann-Whitney test) were considered significant.

[http://www.R-project.org]).

3. Results

3.1. Patient characteristics

A total of 414 patients were included in the study, 322 (78%) of whom had definite IE according to the modified Duke criteria (Table 1). The patients were predominantly male (72.8%). The median age of patients in the cohort was 73.2 years (interquartile range [IQR] 61.3-80.9). Native valves were affected in 70.6% of cases. The aortic valve was the most commonly involved native valve (60%) and also the most commonly affected in the prosthetic valve group (75%).

3.2. Microbiological findings

The causative microorganisms isolated from BC are described in Table 2. Streptococci isolates were identified in all cases and

Table 2
Streptococci species isolated in *Streptococci*-related-infectious endocarditis.

Streptococci species	Number of strains (%)
***Viridans* group streptococci (VGS)**	217 (52.4)
S. mitis/oralis group	87 (21)
S. sanguinis	37 (8.9)
S. gordonii	29 (7)
S. salivarius	15 (3.6)
S. mutans	13 (3.1)
S. anginosus	9 (2.1)
S. pneumoniae	7 (1.7)
S. constellatus	6 (1.4)
S. parasanguinis	4 (1)
S. milleri	3 (0.7)
S. canis	2 (0.5)
Abiotrophia defectiva	2 (0.5)
S. vestibularis	1 (0.3)
S. sobrinus	1 (0.3)
S. intermedius	1 (0.3)
***Streptococcus bovis-equinus* group (SBG)**	144 (34.5)
S. gallolyticus	121 (29.2)
S. bovis	11 (2.7)
S. equinus	5 (1.2)
S. lutetiensis	3 (0.7)
S. infantarius	3 (0.7)
Beta-hemolytic streptococci:	
S. agalactiae	29 (7)
S. dysgalactiae	18 (4.3)
S. pyogenes	6 (1.4)

viridans group *Streptococci* (VGS) were the most commonly identified (52.4%). Among them, *Streptococcus mitis/oralis* group was the most frequently identified species (21%). Within the *bovis-equinus* group *Streptococci* (BGS) (34.5%), *Streptococcus gallolyticus* was the most common species (29.2%).

Furthermore, the source of infection was identified in 62% of cases.

3.3. Treatment and outcome

Antibiotic therapy was reported for 407 (98.3%) patients, with 111 (26.8%) patients prescribed monotherapy. Combined antibiotic therapy was administered for 294 (71.2%) patients, with an association to gentamicin for 282 (68.1%) patients. However, the duration of dual therapy was not available. The most commonly prescribed antibiotic therapies were amoxicillin, third-generation cephalosporins (Cefotaxim, ceftriaxone), vancomycin and cefazolin in 348 (84%), 50 (12.1%), 8 (1.9%) and 1 (0.2%) cases, respectively.

Surgery was indicated according to current guidelines [7] in 196 (47%) patients and performed in 155 (37%) of these patients. Mortality due to streptococcal IE during hospitalisation was 18%. Comparing the characteristics of the 74 (18%) patients who died with the 340 (82%) who survived (Table 3), the median age was similar (74.9 vs. 72.2 years) but there were differences in MIC results. *Streptococci* with MICs of amoxicillin of 0.125–2 mg/L were significantly more frequent in the deceased group of patients ($P = 0.04$). Furthermore, patients with indication for surgery but who did not undergo surgery showed higher in-hospital mortality (20.3% vs. 7.6%) ($P = 0.001$).

Characteristics of patients according to penicillin susceptibility of *Streptococci* isolated in IE are presented as supplemental data (Supplemental Table 1).

Valve status, systemic embolisation, delays for negative BC, source of infection, treatment duration and combined antibiotic therapy were not associated with in-hospital mortality.

Table 3
Risk factors for in-hospital mortality.

	Alive N (%)	Deceased N (%)	Univariate analysis *P*-value	Multivariate analysis *P*-value	OR (95%CI)
Total	340 (100)	74 (100)			
Demographic data					
Males	249 (73.2)	53 (71.6)	0.77		
Median age (y) [range]	72.2 [60.7 – 80.9]	74.9 [67 – 80.4]	0.82		
Type of endocarditis					
NVE	246 (72.4)	47 (63.5)	0.15	0.68	
PVE	84 (24.7)	23 (31.1)	0.3		
Device-related endocarditis	10 (2.9)	4 (5.4)	0.28		
Comorbidities					
Diabetes	62 (18.2)	21 (28.4)	**0.05**	0.44	
Renal insufficiency	85 (25)	26 (35.1)	0.08	0.74	
Valve involved					
Aortic	185 (54.4)	37 (50)	0.52		
Mitral	125 (36.7)	28 (37.8)	0.89		
Tricuspid	13 (3.8)	3 (4)	1		
Pulmonary	1 (0.3)	0 (0)	1		
ICED	12 (3.5)	3 (4)	1		
Unknown	4 (1.2)	3 (4)	0.11		
Complications					
Embolism	55 (16.2)	32 (43.2)	**<0.01**	0.55	
MIC Amoxicillin					
≤0.125 mg/L	172 (50.6)	26 (35.1)	**0.04**	0.72	
0.25 – 2 mg/L	119 (35)	42 (56.7)	**<0.01**	**0.04**	2.23 [1.03 – 4.88]
Presumed source of infection					
Oral	112 (32.9)	15 (20.2)	**0.03**	0.08	
Non-oral gastrointestinal tract	74 (21.8)	18 (24.3)	0.64		
Other	23 (6.8)	4 (5.4)	0.72		
Unknown	131 (38.5)	37 (50)	0.08		
Treatment					
Combined antibiotic therapy	240 (70.5)	42 (56.7)	0.027		
Indication for surgery	161 (47.3)	35 (47.3)	1		
Surgery performed	135 (39.7)	20 (27)	**0.04**	**0.001**	0.23 [0.1 – 0.56]

CI: confidence interval, ICED: intra-cardiac electronic device, ICU: intensive care unit, MIC: minimal inhibitory concentration, NVE: native valve endocarditis, OR: odds ratio, PVE: prosthetic valve endocarditis

4. Discussion

Gram-positive cocci, mainly *Streptococci* and *Staphylococci*, remain the major cause of IE. This study showed the long-standing predominance of VGS has progressively faded in *Streptococci*-related IE, whereas the number of cases caused by BGS has increased, accounting for 34.8% (144/414) of all cases of *Streptococci*-related IE.

These study results show that in France, VGS is the prime cause of *Streptococci*-related IE with a higher incidence than for BGS according to the results of the ICE-PCS cohort [7]. This situation is similar in the majority of US and European hospitals.

Data on the correlation between mortality in *Streptococci*-related IE and increased MICs to beta-lactams are limited and most of them reported penicillin sensitivity. Thus, among patients with bacteraemia, patients with *Streptococci*-related IE with high MICs for penicillin have been shown to have worse outcome compared with patients infected with penicillin-susceptible strains [8,9]. In another French study, higher MICs of penicillin G were not associated with higher mortality or increased need for surgery [10]**.** For isolates with MICs of penicillin $\geq$ 0.125 mg/L, there is a debate regarding the benefit of combined antibiotic therapy with beta-lactams and aminoglycoside. Knoll et al. reported a retrospective study of 29 patients with VGS-related IE due to either penicillin-susceptible or -resistant strains. Twenty strains were resistant to penicillin G with MICs of 1.0-4.0 mg/L and nine strains presented decreased susceptibility to penicillin G (MIC 0.5 mg/L). Ten patients had prosthetic valve endocarditis, nine of whom were treated with a combination of beta-lactam and aminoglycoside, and all patients survived. These data do not prove that combination therapy with an aminoglycoside has greater efficacy but they indicate that such a combination is likely to be curative [11]. These studies analyse susceptibility to penicillin G even though amoxicillin is the most commonly prescribed drug in Europe for *Streptococci*-related IE. Our study is the first to show a significant relationship between mortality from *Streptococci*-related IE and increased MICs to amoxicillin.

Penicillin-resistant strains of VGS are prevalent in countries with high incidence of penicillin-resistant *Streptococcus pneumoniae*, as reported in Taiwan [12]. Conversely, there were no differences in patient characteristics, local complications, systemic embolisation, surgery and in-hospital mortality between endocarditis caused by penicillin-susceptible *S. pneumoniae* and endocarditis caused by penicillin-resistant *S. pneumoniae* [13].

Penicillin resistance is most often described in several species of oral *Streptococci* but previous reports showed heterogeneity in antibiotic susceptibilities among *Streptococci* species. Previous studies have shown a decreased susceptibility to penicillin in *Streptococci*, with high levels of beta-lactam resistance particularly in oral-borne *Streptococci* [14]. This could be partly explained by Penicillin Binding Protein (PBP) genes mosaic structure as a result of interspecies horizontal gene transfer events, particularly between commensal VGS and *S. pneumoniae* [15,16]. The most commonly prescribed antibiotics in general practice favour this increased resistance [17].

5. Conclusion

In our multicentre study, VGS constitute the first cause of *Streptococci*-related IE. High-level penicillin resistance in *Streptococci*-related IE has been increasingly described, particularly for VGS. However, the results of this study showed that amoxicillin resistance was associated with higher mortality. Therapeutic strategies are based on consensus conferences but only a few clinical trials have focused on *Streptococci* aetiologies. Further studies are needed to define the best treatment strategies for IE in the context of these emerging resistant strains.

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References

[1] van der Meer JT, Thompson J, Valkenburg HA, Michel MF. Epidemiology of bacterial endocarditis in The Netherlands. II. Antecedent procedures and use of prophylaxis. Arch Intern Med 1992;152:1869–73.

[2] Hoen B, Alla F, Selton-Suty C, Béguinot I, Bouvet A, Briançon S, et al. Changing profile of infective endocarditis: results of a 1-year survey in France. JAMA 2002;288:75–81.

[3] Cabell CH, Jollis JG, Peterson GE, Corey GR, Anderson DJ, Sexton DJ, et al. Changing patient characteristics and the effect on mortality in endocarditis. Arch Intern Med 2002;162:90–4.

[4] Murdoch DR, Corey GR, Hoen B, Miró JM, Fowler VG, Bayer AS, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med 2009;169:463–73. doi:10.1001/archinternmed.2008.603.

[5] Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta J-P, et al., Authors/Task Force Members 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015. doi:10.1093/eurheartj/ehv319.

[6] Poyart C, Quesne G, Trieu-Cuot P. Taxonomic dissection of the Streptococcus bovis group by analysis of manganese-dependent superoxide dismutase gene (sodA) sequences: reclassification of "Streptococcus infantarius subsp. coli" as Streptococcus lutetiensis sp. nov. and of Streptococcus bovis biotype 11.2 as Streptococcus pasteurianus sp. nov. Int J Syst Evol Microbiol 2002;52:1247–55. doi:10.1099/00207713-52-4-1247.

[7] Murdoch DR, Corey GR, Hoen B, Miró JM, Fowler VG Jr, Bayer AS, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med 2009;169:463–73. doi:10.1001/archinternmed.2008.603.

[8] Mrazova M, Docze A, Buckova E, Bucko L, Kacmarikova M, Grey E, et al. Prospective national survey of viridans streptococcal bacteraemia risk factors, antibacterial susceptibility and outcome of 120 episodes. Scand J Infect Dis 2005;37:637–41. doi:10.1080/00365540510043266.

[9] Spanik S, Trupl J, Kunova A, Botek R, Sorkovska D, Grey E, et al. Viridans streptococcal bacteraemia due to penicillin-resistant and penicillin-sensitive streptococci: analysis of risk factors and outcome in 60 patients from a single cancer centre before and after penicillin is used for prophylaxis. Scand J Infect Dis 1997;29:245–9.

[10] Hanslik T, Hartig C, Jurand C, Armand-Lefevre L, Jubault V, Rouveix E, et al. Clinical significance of tolerant strains of streptococci in adults with infective endocarditis. Clin Microbiol Infect 2003;9:852–7.

[11] Knoll B, Tleyjeh IM, Steckelberg JM, Wilson WR, Baddour LM. Infective endocarditis due to penicillin-resistant viridans group streptococci. Clin Infect Dis 2007;44:1585–92. doi:10.1086/518174.

[12] Song J-H, Jung S-I, Ko KS, Kim NY, Son JS, Chang H-H, et al. High prevalence of antimicrobial resistance among clinical Streptococcus pneumoniae isolates in Asia (an ANSORP study). Antimicrob Agents Chemother 2004;48:2101–7. doi:10.1128/AAC.48.6.2101-2107.2004.

[13] Martínez E, Miró JM, Almirante B, Aguado JM, Fernandez-Viladrich P, Fernandez-Guerrero ML, et al. Effect of penicillin resistance of Streptococcus pneumoniae on the presentation, prognosis, and treatment of pneumococcal endocarditis in adults. Clin Infect Dis 2002;35:130–9. doi:10.1086/341024.

[14] Faibis F, Fiacre A, Demachy MC. [Update on the susceptibility of streptococci to antibiotics (enterococci and Streptococcus pneumoniae excluded)]. Ann Biol Clin (Paris) 2003;61:49–59.

[15] Dowson CG, Coffey TJ, Kell C, Whiley RA. Evolution of penicillin resistance in Streptococcus pneumoniae; the role of Streptococcus mitis in the formation of a low affinity PBP2B in S. pneumoniae. Mol Microbiol 1993;9:635–43.

[16] Todorova K, Maurer P, Rieger M, Becker T, Bui NK, Gray J, et al. Transfer of penicillin resistance from Streptococcus oralis to Streptococcus pneumoniae identifies murE as resistance determinant. Mol Microbiol 2015. doi:10.1111/mmi.13070.

[17] Goldsmith CE, Hara Y, Sato T, Nakajima T, Nakanishi S, Mason C, et al. Comparison of antibiotic susceptibility in viridans group streptococci in low and high antibiotic-prescribing General Practices. J Clin Pharm Ther 2015;40:204–7. doi:10.1111/jcpt.12245.