Clinical profile, antibiotic treatment, and risk of stroke in patients with infective endocarditis

Perfil clínico, tratamiento antibiótico y riesgo de ictus en pacientes con endocarditis infecciosa

Dear Editor:

We read with great interest the Letter to the Editor by Martínez-Sellés[1] on the article ''Prevalence of neurological complications in infective endocarditis.''[2]

In response to his comments, the aims of this reply are to analyse in greater depth the comorbidities observed in the patients included in the initial study and to underscore the importance of early antibiotic treatment to reduce the incidence of neurological complications in infective endocarditis (IE).

The retrospective cohort study included 222 patients diagnosed with IE according to the modified Duke criteria.[3] The study population showed a predominance of men in the sixth decade of life presenting mainly aortic and mitral valve involvement. Demographic, clinical, and microbiological variables are shown in Table 1. We should underscore arterial hypertension as the most frequent comorbidity, affecting 128 patients (57.7%), followed by structural heart disease in 93 patients (41.8%), and diabetes mellitus (DM) in 74 patients (33.3%). A total of 9 patients (4%) presented recurrent endocarditis[4], defined as a new episode of IE 2 months after completion of the antibiotic treatment.

As described in the previous study[2], ischaemic stroke was the most frequent neurological complication (35 patients, 15.8% of the total sample). Haemorrhagic stroke was the second most frequent complication (11 patients, 4.9%).

Table 2 compares demographic, clinical, and microbiological data in patients with and without stroke. A further analysis of patients' clinical profiles revealed that the subgroup of patients with stroke (*n* = 46) presented a higher prevalence of DM and smoking than the remaining patients (43.5% vs 30.7% and 32.6% vs 9.7%, respectively), although these differences were not statistically significant. In the subgroup of patients with ischaemic stroke (*n* = 35), we more frequently observed *Staphylococcus aureus* infection as the pathogenic agent (34.2% vs 22.7%) and a more frequent involvement of the mitral valve (51.4% vs 42.6%), although these differences were not statistically significant.

Table 1 Demographic, clinical, and microbiological variables in patients with infective endocarditis.

Variable	Patients with IE (*n* = 222)
Men, *n* (%)	148 (66.7)
Age in years, mean (SD)	66.4 (14.2)
Comorbidities, *n* (%)	
Arterial hypertension	128 (57.7)
Diabetes mellitus	74 (33.3)
Dyslipidaemia	57 (25.7)
Atrial fibrillation	56 (25.2)
Heart failure	35 (15.7)
Structural heart disease	93 (41.8)
Chronic kidney disease	47 (21.2)
Active smoking	32 (14.4)
Parenteral consumption of drugs	7 (3.2)
Active neoplasm	35 (15.8)
Previous IE	9 (4.0)
Community origin, n (%)	168 (75.7)
Prosthetic valve, n (%)	55 (24.8)
Prosthesis location, n (%)	
Aortic	30/55 (54.6)
Mitral	13/55 (23.6)
Mitral-aortic	12/55 (21.8)
Vegetation location, n (%)	12/55 (21.8)
Aortic	91 (41)
Mitral	96 (43.2)
Mitral-aortic	24 (10.8)
Tricuspid	8 (3.6)
Not identified	3 (1.4)
Microorganism, n (%)	
Staphylococcus aureus	54 (24.3)
Staphylococcus epidermidis	24 (10.8)
Streptococci	57 (25.7)
Enterococci	21 (9.5)
Gram-negative	21 (9.5)
Other	19 (8.5)
Negative blood cultures	26 (11.7)
Emergency surgery, *n* (%)	44 (19.8)
Time between admission and diagnosis in days, median (Q_1—Q_3)	4.39 (2—10)
Hospital stay in days, median (Q_1—Q_3)	31.5 (14—49)
In-hospital mortality, *n* (%)	78 (31.1)
Time until death in days, median (Q_1—Q_3)	18 (9—33)

IE: infective endocarditis; Q_1—Q_3: quartiles 1 and 3; SD: standard deviation.
Modified from Rodríguez-Montolio et al.[2]

Table 2 Demographic, clinical, and microbiological variables in patients with infective endocarditis, by subgroup.

Variable	Patients with stroke (n = 46)			Patients without stroke (n = 176)	P
	Ischaemic stroke (n = 35)	Haemorrhagic stroke (n = 11)	Total		
Men, n (%)	24 (68.6)	6 (54.5)	30 (65.2)	118 (67)	ns
Age in years, mean (SD)	65.6 (10.9)	59.7 (10)	64 (11.6)	66.6 (15)	ns
Comorbidities, n (%)					
Arterial hypertension	18 (51.4)	7 (63.6)	25 (54.3)	103 (58.5)	
Diabetes mellitus	16 (45.7)	4 (36.3)	20 (43.5)	54 (30.7)	
Dyslipidaemia	6 (17.1)	2 (18.2)	8 (17.4)	49 (27.8)	
Atrial fibrillation	10 (28.6)	2 (18.2)	12 (26.1)	44 (25)	
Heart failure	6 (17.1)	2 (18.2)	8 (17.4)	27 (15.3)	
Structural heart disease	13 (37.1)	3 (27.3)	16 (34.8)	77 (43.8)	ns
Chronic kidney disease	5 (14.3)	2 (18.2)	7 (15.2)	40 (22.7)	
Active smoking	10 (28.6)	5 (45.5)	15 (32.6)	17 (9.7)	
Parenteral consumption of drugs	1 (2.9)	0 (0)	1 (2.2)	6 (3.4)	
Active neoplasm	5 (14.3)	4 (36.4)	9 (19.6)	26 (14.8)	
Previous IE	1 (2.9)	0 (0)	1 (2.2)	8 (4.5)	
Community origin, n (%)	29 (82.9)	8 (72.7)	37 (80.4)	131 (74.4)	ns
Prosthetic valve, n (%)	8 (22.9)	2 (18.2)	10 (21.7)	45 (25.7)	ns
Prosthesis location, n (%)					
Aortic	3/8 (37.5)	2/2 (100)	5/10 (50)	26/45 (57.8)	
Mitral	2/8 (25)	0 (0)	2/10 (20)	11/45 (24.4)	ns
Mitral-aortic	3/8 (25)	0 (0)	3/10 (30)	8/45 (17.8)	
Vegetation location, n (%)					
Aortic	11 (31.5)	6 (54.5)	17 (37)	74 (42.1)	
Mitral	18 (51.4)	3 (27.3)	21 (45.6)	75 (42.6)	
Mitral-aortic	4 (11.3)	2 (18.2)	6 (13)	18 (10.2)	ns
Tricuspid	1 (2.9)	0 (0)	1 (2.2)	7 (4)	
Not identified	1 (2.9)	0 (0)	1 (2.2)	2 (1.1)	
Microorganism, n (%)					
Staphylococcus aureus	12 (34.2)	2 (18.2)	14 (30.4)	40 (22.7)	
Staphylococcus epidermidis	3 (8.6)	2 (18.2)	5 (10.9)	19 (10.8)	
Streptococci	9 (25.7)	3 (27.3)	12 (26.1)	45 (25.6)	
Enterococci	3 (8.6)	0 (0)	3 (6.5)	18 (10.2)	ns
Gram-negative	4 (11.4)	3 (27.3)	7 (15.2)	14 (8)	
Other	1 (2.9)	1 (9.1)	2 (4.3)	17 (9.7)	
Negative blood cultures	3 (8.6)	0 (0)	3 (6.5)	23 (13)	
Emergency surgery, n (%)	9 (25.7)	3 (27.3)	12 (26.1)	32 (18.2)	ns
In-hospital mortality, n (%)	17 (48.6)	6 (54.5)	23 (50)	55 (31.3)	.025

IE: infective endocarditis; ns: not significant; SD: standard deviation.

The in-hospital mortality rate was higher in the subgroup of patients with stroke (31.3% vs 50%, P = .025) and slightly higher in the group of patients with haemorrhagic stroke than in those with ischaemic stroke (54.5% vs 48.6%).

In terms of antibiotic treatment, all patients were treated with antimicrobial therapy in accordance with the recommendations of clinical practice guidelines[3]. Given the retrospective nature of the study and the lack of specific data for patients diagnosed prior to the implementation of electronic clinical records, we are unable to determine the distribution of the time of onset of neurological symptoms with regards to antibiotic therapy. However, we did observe that 35/46 patients (76.1%) presented neurological symptoms before antibiotic therapy onset or during the first days thereafter.

Neurological complications, and especially ischaemic stroke, are the most frequent extracardiac complications in IE and are associated with high rates of morbidity and mortality[5–7]. It is important to identify risk factors associated both with ischaemic and with haemorrhagic stroke in IE in order to optimise the early clinical management of patients and to improve their functional and vital prognosis.

Regarding ischaemic stroke, mitral valve involvement and the participation of *S. aureus* as aetiological agent have previously been identified as risk factors[5–7]. These data are similar to those described in our study, although we found no statistically significant association. We also underscore the higher prevalence of DM in the subgroup of patients with ischaemic stroke, as was observed in the study by Valenzuela et al.[6] and in accordance with the comments by Martínez-Sellés[1].

Regarding haemorrhagic stroke, the study by Valenzuela et al.[6] identified male sex, rheumatic heart disease, and fungal infection as risk factors. In our study, we observed a higher percentage of smokers in this subgroup of patients, although smoking has not previously been described as a risk factor, and the difference was not statistically significant.

Embolic events are one of the main causes of morbidity and mortality in IE, and usually occur before or during the first week of antibiotic therapy[7]. In our study, 76.1% of patients with stroke presented neurological symptoms before onset of antibiotic therapy or during the first days; similar data were reported by García-Cabrera et al.[5] (86%) and Valenzuela et al.[6] (80%). Given the previously described limitations of our study, we could not analyse the incidence and the decrease in neurological events during antibiotic therapy. However, other studies have shown that the risk of embolism decreases by approximately 50% after one week of effective antibiotic therapy; therefore, early treatment onset is fundamental[3,7,8]. We believe that a multidisciplinary approach to patients with IE is essential to optimising its management and treatment and to reducing the morbidity and mortality associated with the condition and its embolic complications.

References

1. Martínez-Sellés M. Perfil clínico, tratamiento antibiótico y riesgo de ictus en pacientes con endocarditis infecciosa; 2022, http://dx.doi.org/10.1016/j.nrl.2022.06.010.
2. Rodríguez-Montolio J, Meseguer-Gonzalez D, Almeida-Zurita M, Revilla-Martí P, Santos-Lasaosa S. Prevalencia de las complicaciones neurológicas en la endocarditis infecciosa. Neurología. 2022, http://dx.doi.org/10.1016/j.nrl.2021.09.013, in press.
3. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta J-P, Del Zotti F, et al. ESC Guidelines for the management of infective endocarditis. European Heart Journal. 2015;36:3075—123. Current European guidelines for diagnosis and management of infective endocarditis.
4. Rodríguez M, Anguita M, Castillo JM, Torres F, Siles JR, Mesa D, et al. Características clínicas y evolución de la endocarditis infecciosa recurrente en no drogadictos. Rev Esp Cardiol. 2001;54(9):1075—80. Spanish.
5. García-Cabrera E, Fernández-Hidalgo N, Almirante B, Ivanova-Georgieva R, Noureddine M, Plata A, et al. Neurological complications of infective endocarditis: risk factors, outcome, and impact of cardiac surgery: a multicenter observational study. Circulation. 2013;127:2272—84.
6. Valenzuela I, Hunter MD, Sundheim K, Klein B, Dunn L, Sorabella R, Han SM, Willey J, George I, Gutierrez J. Clinical risk factors for acute ischaemic and haemorrhagic stroke in patients with infective endocarditis. Intern Med J. 2018;48:1072—80.
7. Dickerman SA, Abrutyn E, Barsic B, Bouza E, Cecchi E, Moreno A, et al. The relationship between the initiation of antimicrobial therapy and the incidence of stroke in infective endocarditis: an analysis from the ICE Prospective Cohort Study (ICE-PCS). Am Heart J. 2007;154:1086—94.
8. Vincent LL, Otto CM. Infective endocarditis: Update on epidemiology, outcomes, and management. Curr Cardiol Rep. 2018;20:86.

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