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MAJOR ARTICLE

Epidemiology and Risk Factors of Mycotic Aneurysm in Patients With Infective Endocarditis and the Impact of its Rupture in Outcomes. Analysis of a National Prospective Cohort

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Background. Several aspects of the occurrence and management of mycotic aneurysm (MA) in patients with infective endocarditis (IE) have not been studied.

Objectives. To determine the incidence and factors associated with MA presence and rupture and to assess the evolution of those initially unruptured MA.

Methods. Prospective multicenter cohort including all patients with definite IE between January 2008 and December 2020.

Results. Of 4548 IE cases, 85 (1.9%) developed MA. Forty-six (54.1%) had intracranial MA and 39 (45.9%) extracranial MA. Rupture of MA occurred in 39 patients (45.9%). Patients with ruptured MA had higher 1-year mortality (hazard ratio, 2.33; 95% confidence interval, 1.49–3.67). Of the 55 patients with initially unruptured MA, 9 (16.4%) presented rupture after a median of 3 days (interquartile range, 1–7) after diagnosis, being more frequent in intracranial MA (32% vs 3.3%, $P = .004$). Of patients with initially unruptured MA, there was a trend toward better outcomes among those who received early specific intervention, including lower follow-up rupture (7.1% vs 25.0%, $P = .170$), higher rate of aneurysm resolution in control imaging (66.7% vs 31.3%, $P = .087$), lower MA-related mortality (7.1% vs 16.7%, $P = .232$), and lower MA-related sequalae (0% vs 27.8%, $P = .045$).

Conclusions. MA occurred in 2% of the patients with IE. Half of the Mas occurred in an intracranial location. Their rupture is frequent and associated with poor prognosis. A significant proportion of initially unruptured aneurysms result from rupture during the first several days, being more common in intracranial aneurysms. Early specific treatment could potentially lead to better outcomes.

Keywords. complications; epidemiology; infective endocarditis; mortality; mycotic aneurysm.

Mycotic aneurysms (MAs) represent a serious and potentially life-threatening complication of infective endocarditis (IE) [1, 2]. They arise from septic arterial embolization to the vasa vasorum, leading to arterial wall infection, destruction, and subsequent aneurysmal dilation [3]. Because of the friable infected arterial wall, MAs present a high risk of rupture, which conveys elevated mortality and prevalence of sequalae among survivors, especially in patients with intracranial MA [4]. Despite their influence on the prognosis of the patient, several aspects of the occurrence and management of MA in patients with IE have not been well studied and there are several knowledge gaps regarding the epidemiology, risk factors, clinical presentation, and outcomes associated with MA in this population [3].

First, although the occurrence of MAs in the context of IE has been recognized for decades, its incidence remains uncertain because most of the available literature on MAs is small

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case series or case reports, with a very limited number of large-scale studies specifically focused on this topic [5].

Second, 1 of the key challenges in managing patients with MA in the context of IE lies in the timely diagnosis. Initial presentation of unruptured MA is often subtle [1, 6]. Accordingly, identification of risk factors of MA formation could be important for performing diagnostic tests in patients at risk before rupture occurs [1]. However, the factors associated with MA development in the setting of IE have not been studied.

Third, optimal treatment strategies for patients with MAs are another area of uncertainty. Ruptured aneurysms must be treated urgently [3, 7]. However, because of the lack of studies on the treatment of unruptured MAs and the lack of identification of the factors associated with rupture in those initially unruptured MAs, there is no agreement on the best treatment strategy (specific intervention or antibiotics alone) for an unruptured MA [1, 3, 4, 7–11].

To address these knowledge gaps, we conducted a comprehensive study using data from the Spanish Collaboration on Endocarditis registry (GAMES is its Spanish abbreviation), which has been proven useful for endocarditis research [12–15]. By analyzing a large, national cohort of patients with IE, we aimed to determine the incidence and factors associated with MA presence, in addition to the factors associated with rupture. Furthermore, we aimed to assess the evolution of those MAs initially unruptured and the impact of early, specific treatment, either surgical or endovascular, in this scenario.

By addressing these key knowledge gaps, our study aims to contribute to the existing literature on MAs in patients with IE and provide insights that can guide clinical decision-making and improve patient care. Ultimately, a better understanding of the epidemiology, risk factors, clinical implications, and optimal management strategies for MAs in the context of IE has the potential to improve outcomes and reduce the burden of this severe complication.

PATIENTS AND METHODS

Between January 2008 and December 2020, consecutive patients with definite IE according to the Duke modified criteria were prospectively included in GAMES. This registry is maintained by 42 Spanish hospitals. Cohort registration was approved by regional and local ethics committees, and all patients signed informed consent.

At each center, a multidisciplinary team completes an anonymized and standardized form with the IE episode and a follow-up form after 1 year. Demographic, clinical, microbiological, echocardiographic, and prognostic sections are included in the forms. These standardized forms include information regarding the presence or absence of mycotic aneurysm, as well as its location and the presence of rupture.

Among the patients with MA, we retrospectively collect an additional ad hoc form including variables related to MA clinical presentation, specific treatment received, and MA-related mortality and sequelae.

Patients

Patients were categorized according to the presence or absence of MA. Among patients with MAs, they were subcategorized according to MA location (intracranial MA or extracranial MA), and the presence of rupture (ruptured MA and unruptured MA). Additionally, patients with initially unruptured MAs were divided according to the presence or absence of rupture during follow-up.

Decision on performing diagnosis tests and specific treatment was made by a local multidisciplinary team (ie, endocarditis team) on a case-by-case basis.

Definitions

IE was defined using the 2015 European Cardiac Society modified Duke criteria [1]. Microbiological diagnosis was determined by blood or valve culture. Hospital-acquired, non–healthcare-related, and community-acquired IE definitions from previous studies were followed [16]. Chronic renal failure was defined as a previous serum creatinine level >1.4 mg/dL. Worsening or new-onset renal impairment was defined as a worsening of at least 25% of creatinine clearance, as measured by Cockcroft-Gault equation. All necessary variables were collected to calculate the Charlson Comorbidity Index [17]. Persistent bacteremia was defined as positive blood cultures more than 7 days after effective antibiotic therapy. Relapses were defined as a new episode of IE caused by the same microorganism during the first year of follow-up [13]. Surgical indications followed the latest European guidelines [1]. A direct identification was made of patients who had surgical indication but were not operated.

In-hospital mortality and 1-year mortality were defined as death from any cause during hospital admission and at 365 days, respectively. MA-related mortality was defined as in-hospital mortality related or at least influenced by the presence of MA or its complications (eg, ruptured, thrombosis, compression of local structures), as considered by local researchers in the specific ad hoc form. MA-related sequalae was defined as the presence of long-term complication directly associated with the presence of MA or its complications, as considered by local researchers in the specific ad hoc form.

Statistical Analysis

Qualitative variables are expressed as absolute numbers and percentages. Quantitative variables are expressed as median and interquartile range (IQR).

For univariate analyses, categorical variables were compared using χ^2 or Fisher test when necessary, and quantitative variables were compared using Mann-Whitney's U test.

For the multivariate comparison of risk factors for MA, those variables with $P < .10$ in univariate analysis and that were

considered clinically significant, were included in a multivariate logistic regression model, with a maximum of 1 variable for every 10 events (MAs) [18]. Adjusted odds ratios (OR) and its 95% confident intervals (95% CI) are provided.

Additionally, to estimate the effect of MAs on mortality, a multivariate regression Cox analysis was planned, with 1-year mortality as the dependent variable. Independent variables included the presence of MA, MA rupture, and those variables with $P < .10$ in univariate analysis that were considered clinically significant, with a maximum of 1 variable for every 10 MAs [19]. Survival curves were obtained, and adjusted hazards ratios (HR) and 95% CIs are provided.

Bilateral P value < .5 was considered significant. All statistical analyses were performed with SPSS version 25 software (SPSS INC., Chicago, Illinois, USA).

RESULTS

Of a total of 4548 definite IE cases, 85 patients (1.9%) had 92 MAs. Seven patients had multiple MAs. Of these, 46 patients had intracranial MAs (54.1%) and 39 had extracranial MAs (46.9%), with no patients having both extracranial and intracranial MAs. The patients' flowchart is presented in Supplementary Figure 1. Specific locations of the MAs, when available, is presented in Table 1. Of the intracranial MAs, the most common location was medium cerebral artery (66.6%, 22 of 33 cases available). Among extracranial MAs, the most common locations were intraabdominal arteries (39.5%, 15 of 39 cases available) and inferior limbs (28.9%, 11 of 38 cases available). Of note, 7 patients had right-sided IE and MA, with 6 of these cases being pulmonary MAs and the other intraabdominal.

Table 1. Mycotic Aneurysm Specific Location

Location	Number	Percentage
Intracranial (n = 33)		
Medium cerebral artery	22	66.6
Posterior cerebral artery	6	18.2
Vertebrobasilar arteries	3	9.1
Anterior cerebral artery	2	6.1
Extracranial (n = 38)		
Abdominal	15	39.5
Mesentery artery	4	10.5
Abdominal aorta	4	10.5
Splenic artery	2	5.3
Renal arteries	2	5.3
Hepatic artery	1	2.6
Other intraabdominal location	2	5.3
Inferior limb	11	28.9
Pulmonary	6	15.8
Superior limb	5	13.2
Carotid artery	1	2.6

In 14 patients, information about aneurysm specific location could not be retrieved (16.5% of the total), including 13 of the 46 patients with intracranial aneurysm (28.3%) and 1 of the 39 patients with extracranial aneurysm (2.6%)

Factors Associated With the Occurrence of Mycotic Aneurysms

Characteristics of patients with and without MAs are presented in Table 2. Patients with MAs were younger (median 61 years (IQR 43.73) versus 69 years [IQR 57–77], $P < .001$) but with more comorbidity (median Charlson Index 3 [IQR 2–6] versus 2 [IQR 1–4], $P = .003$). They had more frequently community-acquired IEs (75.3% vs 63.2%, $P = .022$) and native valve IEs (75.3% vs 62.9%, $P = .019$). Additionally, patients with MAs had more frequent *Candida* endocarditis (4.7% vs 1.6%, $P = .049$). The multivariate logistic regression model of factors associated with MA is shown in Table 3. Factors independently associated with MAs were younger age (OR, 0.86 per 5 years older; 95% CI, .80–.94), *Candida* spp. (OR, 4.90; 95% CI, 1.67–14.40) and no known etiology (OR, 3.01; 95% CI, 1.25–7.25).

Factors associated specifically with intracranial or extracranial MAs are summarized in Supplementary Tables 1 and 2, respectively. Of note, factors associated with intracranial MAs were age (59 years [IQR, 43–70] versus 69 [IQR, 57–77], $P < .001$), community-acquired IE (76.1% vs 63.2%, $P = .049$), native valve IE (80.4% vs 62.9%, $P = .014$), mitral valve IE (67.4% vs 44.0%, $P = .001$), and Charlson Index (median 3 vs 2, $P = .006$), whereas factors associated with extracranial MAs were male sex (82.1% vs 67.9%, $P = .060$), right-sided IE (18.0% vs 7.4%, $P = .023$), *Candida* IE (7.7% vs 1.6%, $P = .024$), and the absence of known etiology (10.3% vs 2.9%, $P = .026$). Multivariate logistic regressions models are presented in Tables 4 and 5, respectively. Factors independently associated with intracranial MA were younger age (OR, 0.88 per 5 years older; 95% CI, .82–.96) and mitral valve IE (OR, 2.49; 95% CI, 1.31–4.73). Meanwhile, factors independently associated with extracranial MA were right-sided IE (OR, 2.15; 95% CI, 1.05–4.39), *Candida* spp. (OR, 5.00; 95% CI, 1.47–17.02) and no known etiology (OR, 4.21; 95% CI, 1.46–12.13).

Of note, *Staphylococcus aureus* was not associated with MA or with intracranial MA nor extracranial MA specifically.

Factors Associated With the Rupture of Mycotic Aneurysms

Rupture of MA occurred in 39 patients (45.9%). Rupture occurred after a median of 3 days of antibiotic initiation (IQR, 0–15 days).

Table 6 summarizes the characteristics of patients with ruptured and unruptured MAs. Patients with ruptured MAs less frequently had chronic cardiac failure (10.3% vs 47.8%, $P < .001$) and more frequently had mitral valve IE (74.4% vs 32.6%, $P < 0001$). Importantly, rupture occurred in 63.0% of patients with intracranial MA (n = 29/46) versus 25.6% of patients with extracranial MAs (n = 10/39), $P < .001$. There was no other identifiable factor associated with rupture of MA.

Impact of Mycotic Aneurysm in Patient Management and Outcomes.

Table 2 summarizes management and outcomes of patients with and without MAs. Patients with MAs presented more

Table 2. Characteristics of Patients With IE With and Without MA

Variable	MA (n = 85)	No MA (n = 4463)	*P*
Age (y)	61 (43–73)	69 (57–77)	<.001
Gender (male)	75.3% (64)	67.9% (3033)	.151
Acquisition			
Hospital-acquired	20.0% (17)	28.3% (1263)	.092
Non-nosocomial healthcare-related	4.7% (4)	8.5% (380)	.211
Community-acquired	75.3% (64)	63.2% (2820)	.022
Site of infection			
Native valve	75.3% (64)	62.9% (2807)	.019
Prosthetic valve	22.4% (19)	30.7% (1370)	.098
Cardiac device	2.4% (2)	8.6% (383)	.046
Aortic valve	51.8% (44)	52.9% (2362)	.832
Mitral valve	51.8% (44)	44.0% (1964)	.154
Right-side valve	8.2% (7)	7.4% (329)	.817
Comorbidities			
Diabetes mellitus	21.2% (18)	29.1% (1297)	.112
Chronic respiratory disease	15.2% (13)	18.3% (820)	.467
Chronic cardiac failure	30.5% (26)	32.2% (1441)	.740
Cerebrovascular disease	17.6% (15)	12.4% (554)	.149
Chronic renal failure	17.6% (15)	25.6% (1141)	.097
Chronic liver disease	7.6% (6)	9.9% (443)	.380
Injecting drug user	2.3% (2)	2.6% (117)	.878
HIV infection	3.5% (3)	1.8% (84)	.272
Charlson Comorbidity Index (points)	3 (2–6)	2 (1–4)	.003
Etiology			
Staphylococcus aureus	28.2% (24)	24.2% (1080)	.390
Coagulase-negative staphylococci	7.2% (6)	18.8% (839)	.004
Enterococcus spp.	10.6% (9)	15.0% (671)	.255
Streptococcus spp.	36.5% (31)	27.3% (1217)	.060
Candida spp.	4.7% (4)	1.6% (70)	.049
Other etiology	4.7% (4)	7.1% (318)	.522
No etiology	7.2% (6)	2.9% (8129)	.039
Clinical presentation and echocardiographic findings			
Vegetation	80.0% (68)	78.8% (3518)	.793
Valve perforation or rupture	22.3% (19)	15.1% (676)	.067
Pseudoaneurysm	3.5% (3)	6.6% (296)	.253
Perivalvular abscess	12.9% (11)	18.7% (839)	.170
Intracardiac fistula	2.3% (2)	2.7% (123)	.822
Vascular phenomena	20.0% (17)	9.9% (442)	.002
New cardiac murmur	42.4% (36)	34.6% (1542)	.134
Acute cardiac failure	30.6% (26)	42.0% (1873)	.035
Septic shock	12.9% (11)	13.3% (594)	.921
Persistent bacteremia	12.9% (11)	11.7% (520)	.714
Acute renal injury	34.1% (29)	36.7% (1640)	.618
Management and outcomes			
Cardiac surgical indication	76.5% (65)	70.8% (3.158)	.248
Cardiac surgery performed	45.7% (37)	49.1% (2227)	.450
Cardiac surgery indicated not performed	32.9% (28)	21.9% (977)	.015
Antibiotic duration (d)	42 (29–48)	39 (27–46)	.146
Hospital admission (d)	43 (29–68)	36 (22–52)	.006
In-hospital mortality	31.8% (27)	26.8% (1197)	.309
Relapse	5.1% (3/58)	1.5% (51/3266)	.031
Sequelae	36.2% (21/58)	15.1% (496/3266)	<.001

Abbreviations: IE, infective endocarditis; MA, mycotic aneurysm.

Table 3. Multivariable Regression Model Including Factors Associated With Presence of Mycotic Aneurysm

Variable	Odds Ratio	95% Confidence Interval	*P*
Age (per 5 y)	0.86	.80–.94	<.001
Charlson Index (per point)	1.03	.93–1.13	.616
Community-acquired endocarditis	1.52	.88–2.64	.135
Native valve endocarditis	1.46	.86–2.48	.158
Streptococcus spp.	1.40	.85–2.29	.186
Candida spp.	4.90	1.67–14.40	.004
No etiology	3.01	1.25–7.25	.014
Valve perforation or rupture	1.25	.73–2.15	.410

Table 4. Multivariate Logistic Regression Showing Factors Associated With Intracranial Mycotic Aneurysm

Variable	Odds Ratio	95% Confidence Interval	*P*
Age (per 5 y)	0.88	.82–.96	.001
Simple Charlson Index (per point)	0.92	.78–1.07	.275
Streptococcus spp.	1.30	.70–2.41	.410
Native valve endocarditis	1.61	.75–3.46	.221
Mitral valve endocarditis	2.49	1.31–4.73	.005

Table 5. Multivariate Logistic Regression Showing Factors Associated With Extracranial Mycotic Aneurysm

Variable	Odds Ratio	95% Confidence Interval	*P*
Gender (male)	2.23	.98–5.08	.056
Right-side endocarditis	2.15	1.05–4.39	.035
Candida spp.	5.00	1.47–17.02	.010
No etiology	4.21	1.46–12.13	.008

days of hospital admission (43 [IQR 29–68] versus 36 [22–52], $P = .006$). Although in-hospital mortality was similar (31.8% vs 26.8%, $P = .309$), patients with MA who survive IE episode had more frequent relapses (5.1% vs 1.5%, $P = .031$) and suffered more frequent sequelae (36.2% vs 15.1%, $P < .001$). In the multivariate regression Cox model, 1-year mortality was similar to those patients without MA (HR, 1.05; 95% CI, .73–1.53; $P = .788$) (Supplementary Figure 2).

Regarding specific MA location, those with intracranial MAs had higher in-hospital mortality and sequelae than those without MAs: 37.0% versus 26.8%, $P = .067$; and 51.7% versus 15.1%, $P < .001$) (Supplementary Table 1). Meanwhile, those with extracranial MAs had more frequent relapses than those without (6.8% vs 1.5%, $P = .023$) (Supplementary Table 2).

Importantly, patients with ruptured MAs had higher in-hospital and 1-year mortality than those with unruptured MAs: 43.6% versus 21.7%, $P = .031$; and 48.7% versus 21.7%,

Table 6. Characteristics and Evolution of Patients With IE and Ruptured or Unruptured MA

Variable	Ruptured MA (n = 39)	Unruptured MA (n = 46)	*P*
Age (y)	61 (50–72)	61 (39–74)	.815
Gender (male)	69.2% (27)	80.4% (37)	.233
Acquisition			
Hospital-acquired IE	12.8% (5)	26.1% (12)	.128
Non-nosocomial healthcare-related IE	7.7% (3)	2.2% (1)	.231
Community-acquired IE	79.5% (31)	71.7% (33)	.409
Site of IE			
Native valve	84.6% (33)	67.4% (31)	.067
Prosthetic valve	17.9% (7)	26.2% (12)	.369
Aortic valve	41.0% (16)	60.9% (28)	.068
Mitral valve	74.4% (29)	32.6% (15)	<.001
Right-side valve	2.6% (1)	13.0% (6)	.118
Comorbidities			
Diabetes mellitus	20.5% (8)	21.7% (10)	.890
Chronic respiratory disease	7.6% (3)	21.7% (10)	.073
Chronic cardiac insufficiency	10.3% (49)	47.8% (22)	<.001
Cerebrovascular disease	10.3% (4)	23.9% (11)	.100
Chronic renal failure	12.8% (5)	21.7% (10)	.282
Chronic liver disease	2.6% (1)	10.9% (5)	.282
Injecting drug user	2.6% (1)	4.3% (2)	.373
Charlson Comorbidity Index (points)	3 (1–5)	3 (2–7)	.241
Etiology			
Staphylococcus aureus	35.9% (14)	21.7% (10)	.148
Coagulase-negative staphylococci	7.7% (3)	6.5% (3)	.834
Enterococcus spp.	7.7% (3)	13.0% (6)	.424
Streptococcus spp.	35.9% (14)	37.0% (17)	.919
Candida spp.	2.6% (1)	6.5% (3)	.391
No etiology	2.6% (1)	10.9% (5)	.136
Clinical presentation and echocardiographic findings			
Intracardiac complication	30.8% (12)	39.1% (18)	.422
New cardiac murmur	53.8% (21)	32.6% (15)	.048
Acute cardiac failure	28.2% (11)	32.6% (15)	.661
Septic shock	15.4% (6)	10.9% (5)	.537
Persistent bacteremia	7.7% (3)	17.4% (8)	.184
Acute renal injury	38.5% (15)	30.4% (14)	.437
Mycotic aneurysm presentation			
Intracranial	74.4% (29)	37.0% (17)	<.001
Extracranial	25.6% (10)	73.0% (29)	
Maximum aneurysm size (mm)	8 (3–25) (n = 38)	14 (5–34) (n = 31)	.203
Days from antibiotic initiation to MA diagnosis	2 (1–17)	10 (3–19)	.118
Local symptoms	62.0% (24/38)	46.0% (15/31)	.218
Management and outcomes			
Cardiac surgery performed	36.1% (13)	53.3% (24)	.122
Cardiac surgery indicated not performed	41.0% (16)	26.1% (12)	.144
In-hospital mortality	43.6% (17)	21.7% (10)	.031
In hospital MA-related mortality	26.3% (n = 10/37[a])	4.6% (n = 2/43[a])	.010
1-year mortality	48.7% (19)	21.7% (10)	.009
Relapse (among survivors)	0	6.5% (3/36)	.281
Sequelae (among survivors)	54.5% (12/22)	25.0% (9/36)	.023
MA-related sequalae (survivors)	45.5% (10/22)	5.8% (n = 2/34[b])	.005

Abbreviations: IE, infective endocarditis; MA, mycotic aneurysm.

[a]Cause of death could not be determined in 2 patients with ruptured MA and in 3 patients with unruptured MA.

[b]Cause of sequalae could not be determined in 2 patients with unruptured MA.

$P = .009$. They additionally had more frequent sequelae (45.5% vs 5.8%, $P = .005$). MA-related mortality and MA-related sequalae were also higher in those with ruptured MAs (Table 6). In a multivariate Cox regression model, patients with ruptured MAs had higher 1-year mortality than those without MAs (HR, 2.33; 95% CI, 1.49–3.67; $P < .001$), whereas

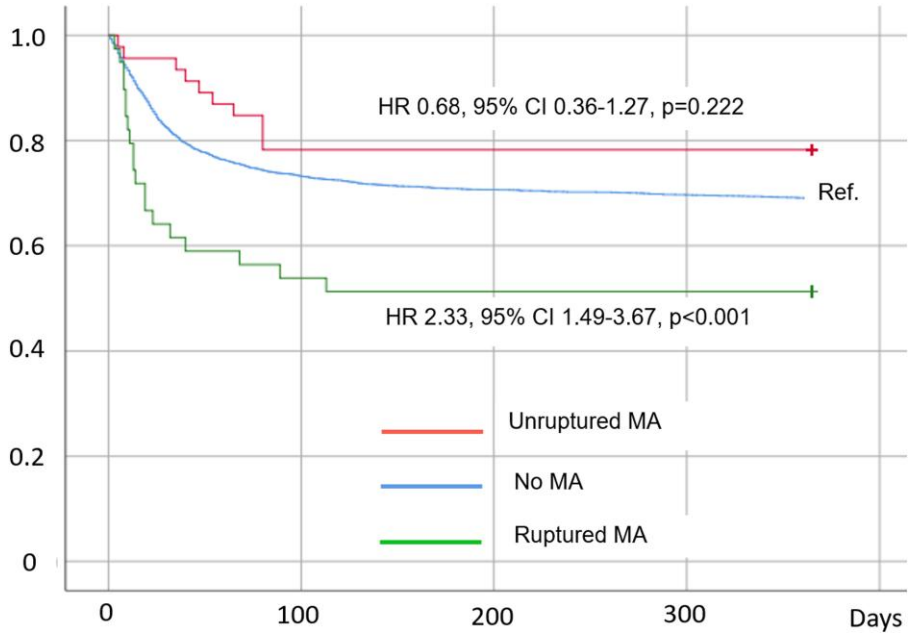

Figure 1. Survival curve for 1-y mortality, obtained by means of multivariate Cox regression model, including absence of mycotic aneurysm, unruptured mycotic aneurysm, and ruptured mycotic aneurysm. Covariates were age (HR, 1.03 per year; 95% CI, 1.02–1.03), Charlson index (HR, 1.12 per point; 95% CI, 1.11–1.15), community-acquired endocarditis (HR, 0.81; 95% CI, .72–.90), natural valve endocarditis (HR, 1.12; 95% CI, .99–1.25), *Streptococcus* spp. (HR, 0.63; 95% CI, .55–.73), *Candida* spp. (HR, 1.41; 95% CI, 1.01–1.97), and valve perforation (HR, 1.17; 95% CI, 1.01–1.37). 95% CI, 95% confidence interval; HR, hazard ratio; MA, mycotic aneurysm.

those with unruptured MAs did not (HR, 0.68; 95% CI, .36–1.27; $P = .22$) (Figure 1).

Outcomes of Initially Unruptured Mycotic Aneurysms

Of the 55 patients with initially unruptured MA (Supplementary Figure 1), 9 (16.4%) presented at least 1 rupture during follow-up. Among these patients, rupture occurred after a median of 3 days (IQR, 1–7) of MA diagnosis. Only in 1 case did the rupture occur later than 7 days after the diagnosis (63 days).

Supplementary Table 3 summarizes characteristics and outcomes of patients with initially unruptured MA according to the presence of rupture during follow-up. Rupture during follow-up was more frequent in intracranial MAs (32% [n = 8/25] versus 3.3% [n = 1/30, $P = .004$]), in patients with staphylococcal IE (31.6% [n = 6/19] versus 8.3% [n = 3/36, $P = .036$]), and in those with mitral valve IE (34.8% [n = 8/23] versus 3.1% [n = 1/32, $P = .002$]). Rupture during follow-up was associated with worse outcomes, including in-hospital mortality (44.4% [n = 4/9] versus 21.7% [n = 10/46, $P = .096$], MA-related mortality (33.3% [n = 3/9] versus 4.6% [n = 2/43, $P = .007$]), and sequelae among survivors (100% [n = 4/5] versus 25.0%]n = 9/36, $P = .001$]).

Treatment of Initially Unruptured Mycotic Aneurysm

Information regarding specific treatment was available in 38 of the 55 patients (69.1%) with initially unruptured MA.

Fourteen (36.8%) patients received specific treatment of the MA before rupture, including 10 patients with endovascular procedure and 4 patients with open surgery. There were no significant differences in age, sex, comorbidities, IE location acquisition, microbiology, or clinical presentation between treated and untreated patients (Supplementary Table 4).

At least 1 rupture during follow-up occurred in 6 untreated patients (25.0%) versus 1 treated patient (7.1%), although the difference did not reach statistical significance ($P = .170$). Additionally, in-hospital mortality and MA-related mortality were numerically higher in untreated patients, though the differences were not statistically significant; 25.0% (n = 6/24) versus 14.3% (n = 2/14), $P = .684$; and 16.7% (n = 4/24) versus 7.1% (n = 1/14), $P = .232$, respectively (Supplementary Table 4). Among survivors, MA-related sequelae were more frequent in untreated patients (27.8% [n = 5/18] versus 0% [n = 0/12, $P = .045$]). None of the untreated patients underwent specific treatment after rupture, whereas the treated patient with rupture during follow-up underwent an additional endovascular procedure.

DISCUSSION

To our knowledge, this is the largest study on MAs in patients with IE. Our main findings are that MAs occur in approximately 2% of patients with endocarditis, with higher prevalence in younger patients and in those with *Candida* endocarditis. Its

rupture occurs in more than half of the cases and its associated with poor prognosis. A significant proportion of initially unruptured aneurysms suffer from rupture during follow-up, with these being more common during the first week after diagnosis and in intracranial mycotic aneurysms. Specific treatment of initially unruptured aneurysms could potentially lead to lower complication rate and better outcomes.

In our nationwide cohort, incidence of MA in patients with IE was near 2%, which is very similar to the incidence of symptomatic MA found by another author [5]. Similar to that study, MAs occurred more frequently in intracranial territory. However, given that unruptured MAs can often be asymptomatic [20, 21] and unruptured MAs can resolve with antibiotics alone [8, 22, 23], the true incidence of MAs in patients with IE is likely underestimated in our study. Of note, in recent studies of routine intracranial image testing in surgical patients, the MA rate was 3%–9% [21, 24, 25], and more than half of the cases had been unsuspected clinically [26].

Our study is the first large cohort to describe factors associated with MA in patients with IE. Notably, risk factors were different for intracranial MA and extracranial MA. Younger age and mitral valve IE were specifically associated with intracranial MA. Our findings are in line with the reported median age (39 years) of patients with intracranial MA in a recent review [4], which can be related to the higher cerebral flow rate in young patients in comparison with the elderly [27, 28]. In addition, Gonzalez et al [5] found a higher proportion of mitral involvement in patients with MA. The reasons for the possible predisposing to intracranial MAs in patients with mitral valve endocarditis are unknown. Accordingly, in our results, a screening diagnostic test could be pursued in those asymptomatic patients at high risk of intracranial MA (ie, young patients with mitral valve endocarditis), especially if cardiac surgery is planned [9, 24, 26].

In contrast, male sex, *Candida* endocarditis, and right-sided endocarditis were associated with extracranial MA. A total of 2.1% (n = 7/336) of patients with right-sided endocarditis had pulmonary MA, with none developing extrathoracic aneurysms (data not shown); this corresponds to the logical spread of embolisms to right-side circulation. On the other hand, the higher burden of atherosclerotic peripheral arteriopathy in male patients could explain the higher proportion of extracranial MA in this subgroup [29, 30]. Finally, *Candida* spp. is known to easily spread and generate secondary embolisms in candidemia episodes [31, 32]. Recognizing these factors can help to maintain a high suspicion index in asymptomatic patients and perform timely diagnostic image testing before rupture occurs.

To our knowledge, this is the first study to describe evolution of initially unruptured peripheral MAs in patients with IE and to compare patient outcomes between those who received MA-specific treatment before rupture or not. Although it is acknowledged that mycotic aortoiliac aneurysm requires rapid intervention [3, 33], there is controversy about the best approach to unruptured peripheral MAs in the context of IE [1–4, 6, 9, 34]. It has not been studied whether specific treatment of these patients, either by endovascular procedure or open surgery [10, 35], could improve their outcomes. Some experts favor a watchful conduct, including serial imaging controls, and performing a specific procedure only when there is an MA growth [1, 3, 6, 11]. However, this management is based only on expert opinion, given that no well-conduct study has been performed to answer this question [36]. In our cohort, we demonstrated that the occurrence of rupture in those MA initially unruptured is relative frequent (approximately 20%) and that it was more common in patients with intracranial MA than in those with extracranial MA (30% vs 3% approximately). Of note, intracranial MAs presented more frequently both at diagnosis and at follow-up rupture in comparison with extracranial MA. Other authors have described case reports and small case-series with initially unruptured intracranial MA with subsequent rupture during follow-up [37–39]. Rice et al found that 44% of intracranial MAs present unfavorable outcomes when managed only with antibiotics [40]. It is not clear why intracranial MA had a higher risk of rupture, but it could be related to the higher flow-rate in comparison with other peripheral arteries of the same diameter, which conveys higher endoluminal pressure [28].

Importantly, in our cohort, both rupture at diagnosis and during follow-up was associated with a much worse prognosis, including higher mortality and chronic sequalae. Accordingly, when we compare outcomes between those who received early MA treatment (ie, before rupture) and those who did not, there was a trend toward better outcomes in the first group, including lower rupture during follow-up (7.1% vs 25.0%, $P = .170$), higher rate of aneurysm resolution in control imaging (66.7% vs 31.3%, $P = .087$), lower MA-related mortality (7.1% vs 16.7%, $P = .232$), and lower MA-related chronic sequalae (0% vs 27.8%, $P = .045$), although the differences were not statistically significant, probably because the low sample size. Nevertheless, it is plausible that early treatment of unruptured MAs could convey better outcomes because of a reduction in the subsequent rupture during follow-up. This could be especially true in patients with intracranial MA, which has higher risk of delay rupture, as previously mentioned. Of note, rupture during follow-up occurred more frequently at initial stages, almost in all cases in the first week after diagnosis and first 2 weeks after antibiotic initiation. Other authors have found higher rates of favorable MA outcomes when the patient had already received a longer antibiotic duration at MA diagnosis [40]. Accordingly, we can hypothesize that specific treatment of unruptured intracranial MA should be pursued urgently and not delayed to decrease the odds of rupture and improve prognosis, as has been proposed by other authors [3, 11, 40].

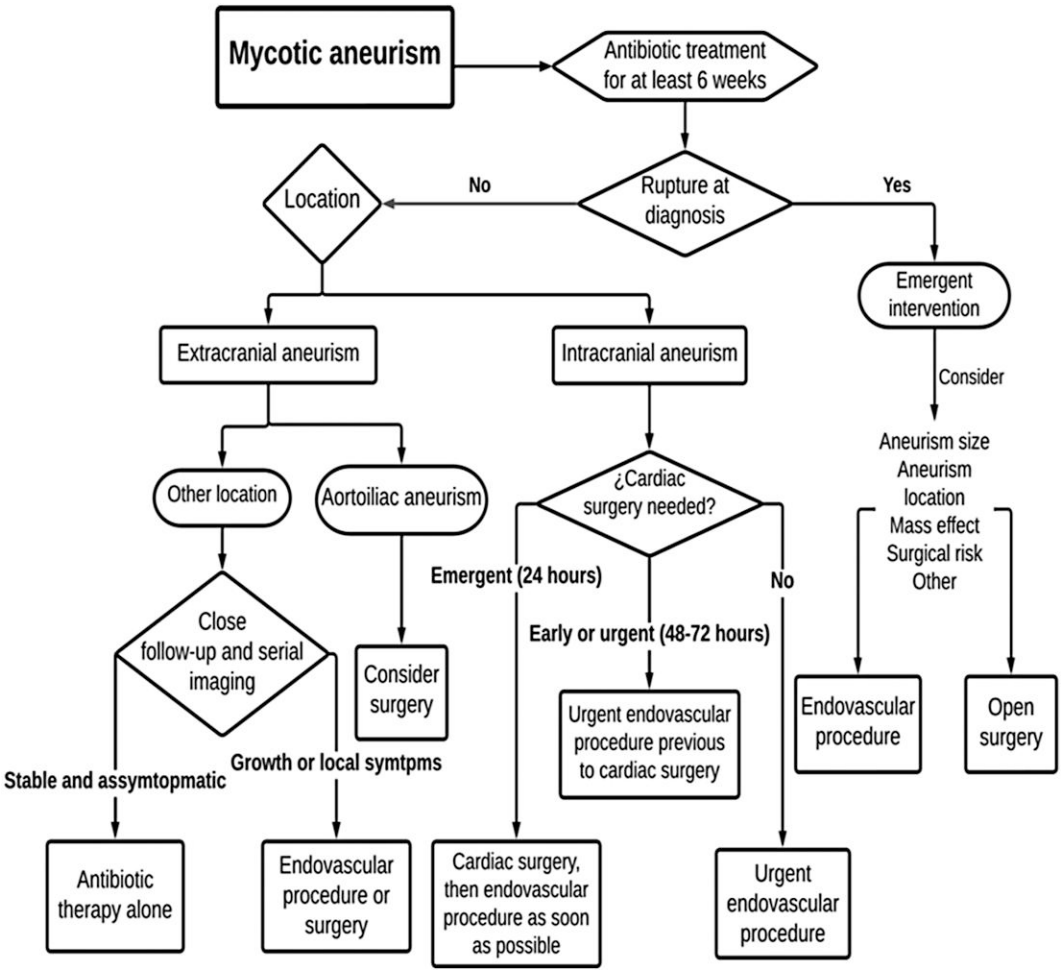

Figure 2. Proposal algorithm for management of mycotic aneurysms in patients with infective endocarditis.

In contrast, the risk of rupture of extracranial MA appears to be lower, and, in these patients, watchful management with close follow-up imaging could be acceptable. Exceptions, in which specific interventions might be carried out, could be extracranial MA localized in large arteries, such as the aorta or common iliac arteries, as recommended elsewhere for patients with an infected aneurysm without IE [3]. In summary, we propose that early specific treatment, preferably by means of endovascular procedure [10, 35, 41], should be carried out in patients with unruptured intracranial MAs urgently. If possible, because of the patient clinical and hemodynamic status, this procedure should be performed before cardiac surgery (if indicated). Meanwhile, for those with unruptured extracranial MA, watchful management with close control imaging could be reasonable. Ruptured MAs, either intracranial or extracranial, should be managed aggressively by means of endovascular procedure or open surgery, depending on location, size, mass effect, and surgical risk [3, 11, 37, 42]. We summarize our proposed algorithm in Figure 2. Nevertheless, we must emphasize that this proposed algorithm is based not only on our data, but also on previous literature and guidelines (ie, the need for surgery in aortoiliac aneurysms). It is not a high-level evidence recommendation, for which it would be necessary to perform larger, prospective, and controlled studies. Yet, those studies might never be obtainable, and we believe that our proposed algorithm is a valuable resource for clinicians treating patients with IE.

Overall, the findings of our study have important clinical implications in the description and management of MAs in patients with IE. However, our work has some limitations that must be mentioned. The most important limitation is that, despite being a nationwide prospective study, it is part of a larger project that has not been specifically designed to analyze MAs. Therefore, there may be several important aspects of this complications that are not properly collected in the database. However, we have tried to mitigate this limitation by retrospectively gathering a specific form including these aspects, which was successful in most of the patients with MAs. Remarkably,

we had no data about the percentage of asymptomatic patients who had undergone contrast imaging to disprove the presence of MAs or the presence of other specific risk factors, such as permeable foramen ovale. Yet, we believe our data add valuable information to available literature. Second, this project takes place in a specific geographical setting, so the generalization of these results to other socioeconomic settings could be limited. Third, part of the statistical analysis, such as multivariate or subgroups analysis, was limited by the relatively small sample size. Yet, our study is the largest cohort of MAs in patients with IE to date, and we believe that our results pose important insights in the occurrence, risk factors, outcomes, and management of patients with this complication. Finally, our study was not a randomized controlled study, and as such, our conclusions regarding therapeutic approaches should be taken with caution. Ideally, larger and randomized studies should be performed to determine which is the best therapeutic option for unruptured MAs. Nevertheless, our study provides evidence for possible benefits of early treatment and could guide design for future research.

In conclusion, MAs are an infrequent but serious complication of IE. They occur in 2% of the cases, with half of the cases being intracranial aneurysms. Younger patients and those with *Candida* endocarditis present higher risk, and those patients with mitral valve endocarditis had higher risk of intracranial aneurysms. The rupture of these aneurysms is frequent and associated with a very poor prognosis. A significant proportion of initially unruptured aneurysms suffer from rupture during the first days after diagnosis, being markedly more common in intracranial aneurysms. Early specific treatment, either by means of endovascular procedure or open surgery, could potentially lead to lower complication rates and better outcomes. Future randomized studies are needed.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Data availability. The data underlying this article will be shared on reasonable request to the corresponding author.

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Dovato
dolutegravir/lamivudine

EVIDENCE SUPPORTS THE HIGH BARRIER TO RESISTANCE OF DOVATO UP TO 5 YEARS[1-3]

CONFIDENCE IN DOVATO ACROSS TREATMENT SETTINGS[4–9]

Treatment-naïve resistance rates, with up to **3 years of evidence**[5–7]

0% (n=0/1,885)*,[4]
REAL-WORLD EVIDENCE

0.1% (n=1/953)**,†,‡,§,5–7
RANDOMISED CONTROLLED TRIALS

Treatment-experienced resistance rates, with up to **5 years of evidence**[1–3]

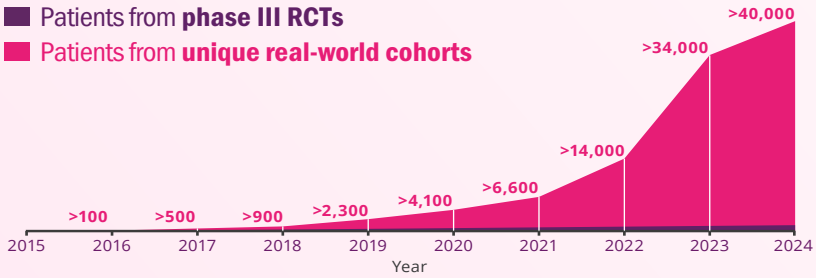
0.03% (n=10/35,888)*,[4]
REAL-WORLD EVIDENCE

0% (n=0/615)||,¶,#,8,9
RANDOMISED CONTROLLED TRIALS

>300,000 PEOPLE LIVING WITH HIV HAVE BEEN TREATED WITH DOVATO GLOBALLY[10]

DOVATO is supported by a wealth of evidence, with the outcomes of **>40,000** people living with HIV captured within clinical trials and real-world evidence, including those with:[4–9,11,12]

- **NO PRIOR TREATMENT EXPERIENCE**[13]
- **NO BASELINE RESISTANCE TESTING**[13]
- **HIGH BASELINE VIRAL LOAD** (>100,000 copies/mL and even >1M copies/mL)[6,13]
- **LOW CD4 + COUNT** (≤200 cells/mm³)[13]



IS IT TIME TO RECONSIDER THE VALUE OF THE 2ND NRTI?

LEARN MORE

DOVATO is indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and adolescents above 12 years of age weighing at least 40 kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine.[13]

Adverse events should be reported. Reporting forms and information can be found at **https://yellowcard.mhra.gov.uk/** or search for MHRA Yellowcard in the Google Play or Apple App store. Adverse events should also be reported to GSK on 0800 221441

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ABBREVIATIONS

3TC, lamivudine; **CD4,** cluster of differentiation 4; **DTG,** dolutegravir; **FDA,** United States Food and Drug Administration; **FTC,** emtricitabine; **HIV,** human immunodeficiency virus; **ITT-E,** intention-to-treat exposed; **NRTI,** nucleoside/nucleotide reverse transcriptase inhibitor; **RCT,** randomised controlled trial; **RNA,** ribonucleic acid; **TAF,** tenofovir alafenamide fumarate; **TDF,** tenofovir disoproxil fumarate; **XTC,** emtricitabine.

FOOTNOTES

*Data extracted from a systematic literature review of DTG+3TC real-world evidence. Overlap between cohorts cannot be fully excluded.

**The reported rate reflects the sum-total of resistance cases calculated from GEMINI I and II (n=1/716, through 144 weeks), STAT (n=0/131, through 52 weeks), and D2ARLING (n=0/106, through 24 weeks).[5–7]

†GEMINI I and II are two identical 148-week, phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority, controlled clinical trials testing the efficacy of DTG/3TC in treatment-naïve patients. Participants with screening HIV-1 RNA ≤500,000 copies/mL were randomised 1:1 to once-daily DTG/3TC (n=716, pooled) or DTG + TDF/FTC (n=717, pooled). The primary endpoint of each GEMINI study was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[13]

‡STAT is a phase IIIb, open-label, 48-week, single-arm pilot study evaluating the feasibility, efficacy, and safety of DTG/3TC in 131 newly diagnosed HIV-1 infected adults as a first line regimen. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 24.[6]

§D2ARLING is a randomised, open-label, phase IV study designed to assess the efficacy and safety of DTG/3TC in treatment-naïve people with HIV with no available baseline HIV-1 resistance testing. Participants were randomised in a 1:1 ratio to receive DTG/3TC (n=106) or DTG + TDF/XTC (n=108). The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48.[7] Results at week 24 of the study.

||The reported rate reflects the sum-total of resistance cases calculated from TANGO (n=0/369, through 196 weeks) and SALSA (n=0/246, through 48 weeks).[8,9]

¶TANGO is a randomised, open-label, trial testing the efficacy of DOVATO in virologically suppressed patients. Participants were randomised in a 1:1 ratio to receive DOVATO (n=369) or continue with TAF-containing regimens (n=372) for up to 200 weeks. At Week 148, 298 of those on TAF-based regimens switched to DOVATO. The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL (virologic non-response) as per the FDA Snapshot category at Week 48 (adjusted for randomisation stratification factor).[8,13]

#SALSA is a phase III, randomised, open-label, non-inferiority clinical trial evaluating the efficacy and safety of switching to DTG/3TC compared with continuing current antiretroviral regimens in virologically suppressed adults with HIV. Eligible participants were randomised 1:1 to switch to once-daily DTG/3TC (n=246) or continue current antiretroviral regimens (n=247). The primary endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[9]

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