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# Clinical course of infectious intracranial aneurysm undergoing antibiotic treatment

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ABSTRACT

*Introduction:* Infectious intracranial aneurysm (IIA, or mycotic aneurysm) is a cerebrovascular complication of infective endocarditis. We aimed to describe the clinical course of IIAs during antibiotic treatment.
*Methods:* We reviewed medical records of persons with infective endocarditis who underwent cerebral angiography at a single tertiary referral center from 2011 to 2016. Aneurysms were followed with subsequent angiography for unfavorable outcome (growth, rupture, no change, or new IIA formation) or favorable outcome (regression or resolution) until endovascular therapy, aneurysm resolution, or end of observation.
*Results:* Of 618 patients included, 40 (6.5%) had 43 IIAs. Eighteen (42%) aneurysms underwent initial endovascular treatment. Twenty-five unruptured aneurysms were followed for a median 18 antibiotic days after IIA discovery (interquartile range [IQR] 4–32). Eleven (44%) aneurysms had unfavorable outcome (1 rupture, 2 new IIA formation, 6 enlargement, and 2 no change) at median 21 days (IQR 5–32). Favorable angiographic outcome was seen in 7 (28%) patients (6 resolution, 1 regression) at median 36 days (IQR 24–41). Seven aneurysms had no angiographic reevaluations but showed no evidence of rupture during clinical follow-up for median 4 days (IQR 3–12) until hospital discharge. Saccular morphology was associated with unfavorable aneurysmal outcome ($p = 0.013$). Longer duration of antibiotic exposure prior to IIA discovery was associated with favorable aneurysmal outcome ($p = 0.046$).
*Conclusion:* IIAs represent a dynamic disease. Only a quarter of IIAs resolve with antibiotics alone. Saccular aneurysmal morphology might predict unfavorable aneurysmal outcome. IIA found after longer antibiotic therapy has higher likelihood of resolution or regression on antibiotic treatment.

## 1. Introduction

Infectious Intracranial aneurysm (IIA, or mycotic aneurysm) is a cerebrovascular complication of infective endocarditis (IE). There is no prospective data demonstrating IIA response to antibiotic treatment alone. Though there is no recommendation for antibiotic treatment duration for IIA, antibiotic treatment generally mirrors that of IE treatment, with duration of antimicrobial therapy commonly extended to 4–6 weeks [1].

In IIA patients undergoing valve replacement surgery for IE, timing of replacement is still unclear [2]. Given intraoperative heparin exposure during valve replacement surgery, there is theoretical increased risk for intraoperative IIA rupture and continued risk of subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH) after valve surgery. Consequently, timely discovery and medical or surgical treatment of IIA has been suggested [3].

The objective of this study was to describe IIA response to antibiotic treatment demonstrated with subsequent angiography. In addition, we aimed to describe if unsecured IIA were at risk for aneurysmal rupture in patients undergoing valve replacement.

## 2. Methods

### 2.1. Study design

The study protocol and ethics were approved by institutional review board prior to collection of data. Data were reported according to strengthening the reporting of observational studies in epidemiology (STROBE) guidelines [4]. No study funding was required given retrospective design. Patients' charts were reviewed retrospectively at our

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tertiary referral center from 2011 to 2016. All patients with IE and digital subtraction angiography (DSA) confirmed IIA were followed for subsequent angiographic outcomes during antibiotic treatment. Standard consent for angiography was obtained for all patients at time of procedure. Final study size was determined by volume of patients with IIA discovered during this time period.

### 2.2. Participants

Inclusion criteria consisted of patients admitted to the hospital with a primary admission diagnosis of IE by Duke Criteria [5] and with DSA confirmed IIA. Indication for DSA included pre-operative clearance for valve surgery or clinical or radiographic concern for SAH. All patients were treated with pathogen directed antibiotics as deemed appropriate by infectious disease specialist. Aneuryms were excluded if thought to be non-infectious, based off prior available vessel imaging, clinical history, and angiographer impression. IIAs were also excluded from analysis of antibiotic response to therapy (primary outcome) if they received initial treatment of their aneurysm prior to serial angiogram (Supplementary Tables 1 and 2). Eligibility for immediate endovascular or surgical treatment upon initial IIA angiographic discovery include need for urgent valve repair, planned valve repair within 2 days, or SAH at presentation. Treatment was at the discretion of the treating endovascular surgeon and vascular neurologist, and may vary based on case complexity, location (eloquent cortex), and patient co-morbidities.

### 2.3. Variables in antibiotic treatment cohort

Initial IIA discovery by DSA was defined as day one. Aneurysms were defined as mycotic if they fell into clinically definite or clinically probable classification proposed by Kannoth et al. in 2009 [3]. Antibiotic treatment days were defined as number of days patient received antibiotics after IIA discovery day one. Exclusion criteria for angiographic follow up in the antibiotic treated cohort included treatment upon IIA discovery using open resection, endovascular clipping, endovascular glue embolization, or endovascular coil embolization. Patients without angiographic follow up were followed clinically for any signs of neurologic deterioration. Unruptured IIA were followed during antibiotic treatment with subsequent DSA for one of two primary outcomes: favorable outcome or unfavorable outcome. Favorable outcome was defined as interval IIA regression or resolution on follow up angiography. Unfavorable outcome was defined as interval angiography with evidence of IIA rupture (or CT/MRI confirmation of new IIA rupture), IIA growth, new IIA formation, or no IIA change despite antibiotic therapy.

Underlying baseline characteristics were collected to compare favorable outcome with unfavorable outcome. Demographic variables collected included age, gender, and race. Cerebrovascular risk factors collected included coronary artery disease, hypertension, diabetes, and hyperlipidemia. Aneurysmal characteristics investigated were IIA morphology (fusiform or saccular), IIA length (mm), IIA width (mm), and IIA proximity. Proximal was defined as 1st or 2nd division of middle cerebral artery (MCA), anterior cerebral artery (ACA), and posterior cerebral artery (PCA) as well as basilar artery, or vertebral artery. Distal was defined as 3rd or 4th division of MCA, ACA, or PCA. Presenting stroke characteristics were defined as ICH, ischemic stroke, or cerebral microbleeds. If patient had available MRI data, this was reviewed in all cases (C.J.R.) for the presence of MRI cerebral microbleeds (CMB) in same territory as angiographically confirmed IIA. CMB were defined as rounded foci of $< 5$ mm in diameter with hypointense signal in susceptibility-weighted image (SWI) which are distinct from vascular flow voids, leptomeningeal hemosiderosis, or non-hemorrhagic subcortical mineralization [6]. All MRI scans included T1-, T2-weighted, Fluid-attenuated inversion recovery (FLAIR), and SWI. In addition, infection and treatment characteristics were collected, including IV drug abuse, causative microorganism, and duration of antibiotic therapy prior to angiographic discovery. Intrinsic valvular characteristics were defined as native or prosthetic, mitral valve, aortic valve, combined mitral and aortic valve, extra-valvular extension, and high grade valve regurgitation ($> 2+$ as measured by cardiologist). Right sided valvular involvement was not analyzed.

### 2.4. Valve surgery cohort

In a separate analysis of all IIA in initial sample, IIAs in patients undergoing valve replacement surgery were followed for perioperative rupture rates of unsecured IIA compared to those with secured IIA. Eligibility for immediate valve repair surgery at our institution include (but are not limited to): moderate to severe progressive heart failure from valve regurgitation, large valve vegetation, aortic root aneurysm/abscess, perforation of valve, recurrent systemic embolization, severe fungal infection, and unstable prosthetic valves. Aneurysms receiving initial endovascular/surgical treatment were not excluded from this analysis. Secured aneurysm was defined as angiographic confirmation of aneurysm resolution prior to valve surgery. Secured IIA was obtained either surgically (through occlusion or clipping/coiling) or with antibiotics (IIA resolution). Perioperative ICH, SAH, and death were compared between patients undergoing valve replacement with unsecured versus secured aneurysms.

### 2.5. Data sources/measurement

All DSAs were initially interpreted by performing angiographer (at time of procedure). A second independent interventional neuroradiologist (J.H.) blinded to previous angiographic impression of outcome reviewed each DSA for confirmation of IIA outcome. Baseline variables were collected by C.J.R, L.Q.Z., S.-M.C, J.K., and R.J.M. Treatment outcomes and analysis were subsequently performed (C.J.R.).

### 2.6. Statistical analysis

Comparisons on demographic, clinical, and imaging characteristics were performed using Fisher's exact test, or Mann-Whitney *U* test to compare baseline patient characteristics described to find statistical correlation for one of the two aneurysmal outcomes defined above. A p-value $< 0.05$ was considered significant. All analysis were conducted using NCSS statistical software 2015 (Kaysville, UT, USA). Graphing performed with Desmos, Inc., online graphing 2018 (San Francisco, CA, USA).

## 3. Results

### 3.1. Aneurysmal outcomes

A total of 618 patients with IE underwent DSA. Forty patients (6.5%) had a total of 43 IIAs (Fig. 1). Eighteen (42%) patients underwent immediate clipping or glue or coil embolization upon IIA initial discovery and were excluded from analysis of the response to antibiotic therapy. Twenty-five (58%) unruptured IIA were followed until favorable or unfavorable outcomes for median 18 antibiotic days after initial discovery (IQR 4–32). Mean diameter on DSA of all IIA was 2.8 mm (SD ± 2.2 mm) × 2.75 mm (SD ± 3.1 mm). Mean diameter for saccular IIA was 2.6 mm ( ± 2.0 mm) × 2.8 ( ± 3.1 mm), and mean diameter for fusiform IIA was 2.8 mm ( ± 2.3 mm) × 2.7 mm ( ± 3.2 mm). Patients undergoing only antibiotic treatment initially did not receive surgical or endovascular therapy for the following reasons: clinician preference for conservative management (n = 20), patient preference for conservative management (n = 1), high risk of vessel sacrifice (n = 4). Seven IIA had favorable outcome (6 resolved, 1 regressed) with a median total antibiotic days from discovery to outcome of 36 (IQR 24–41).Eleven IIAs had unfavorable aneurysmal outcome (1 rupture, 6 enlargement, 2 new IIAs, and 2 no IIA change despite treatment).

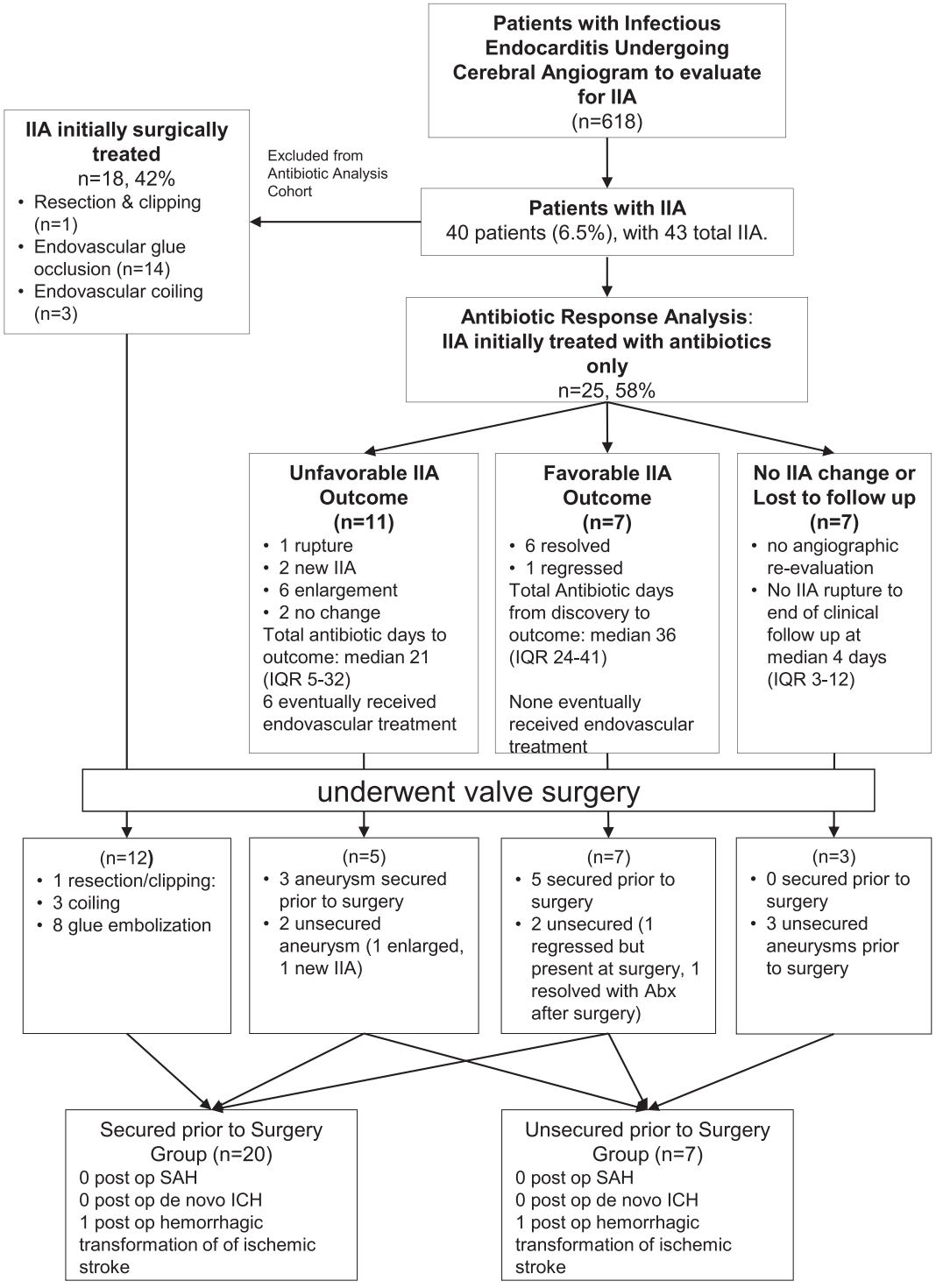


**Fig. 1.** Study design and outcomes.

Median total days of observation to outcome was 21 (IQR 5–32). Seven patients did not have angiographic re-evaluation, and were followed clinically for a median of 4 days (IQR 3–12). No adverse clinical events were recorded in this group.

Baseline demographic and cerebrovascular risk factors were not associated with aneurysmal outcome (Table 1). Characteristics of infection and valves, including the microbe type, prosthetic or native valve, valve function were not associated with outcome, but analysis of antibiotic treatment showed that aneurysms with favorable outcome had longer duration of treatment prior to IIA discovery (median 9 days (IQR 3–12) with favorable outcome, median 1 day (IQR 1–7) with unfavorable outcome, $p = 0.046$). Presenting stroke and brain imaging characteristics of presence of SAH (non-aneurysmal), ICH ischemic stroke, or CMB were not related to aneurysmal outcome on repeat angiography. Notably, IIA morphology of saccular aneurysm morphology was associated with unfavorable aneurysmal outcome ($p = 0.013$), as no mycotic aneurysm with a saccular morphology had a favorable outcome (4 enlarged, 1 with new IIA, 2 no change). IIA characteristics at time of initial IIA angiography showed that location (anterior vs. posterior, $p = 1.0$), vessel proximity (proximal vs. distal, $p = 1.0$), and

**Table 1**
Patient and disease characteristics and aneurysm outcomes.

| | Characteristic | Total | Favorable aneurysmal outcome | Unfavorable aneurysmal outcome | p Value |
|---|---|---|---|---|---|
| | | n = 18 | n = 7 | n = 11 | |
| Demographics and cerebrovascular risk factors | Age median, (IQR) | 45 (33–50) | 51 (41–57) | 41 (33–46) | 0.07 |
| | Mal,e n (%) | 11 (61) | 4 (57) | 7 (64) | 1 |
| | Caucasian, n (%) | 14 (78) | 6 (86) | 8 (73) | 0.63 |
| | Coronary artery disease, n (%) | 1 (5) | 1 (14) | 0 | 0.38 |
| | Hypertension, n (%) | 6 (33) | 4 (57) | 2 (18) | 0.14 |
| | Diabetes mellitus, n (%) | 1 (5) | 1 (14) | 0 | 0.39 |
| | Hyperlipidemia, n (%) | 4 (22) | 3 (43) | 1 (9) | 0.25 |
| Infection characteristics | intravenous drug abuse, n (%) | 8 (44) | 3 (43) | 5 (45) | 1 |
| | *Staphylococcus aureus*, n (%) | 6 (33) | 2 (29) | 4 (36) | 1 |
| | Streptococcus, n (%) | 4 (22) | 3 (29) | 1 (9) | 0.25 |
| | Antibiotic duration to time of IIA discovery, median days (IQR) | 4 (1–15) | 9 (3 − 12) | 1 (1–7) | 0.05 |
| Intrinsic valvular characteristics | Native valve n (%) | 14 (78) | 5 (71) | 9 (82) | 1 |
| | Mitral valve n (%) | 4 (22) | 0 | 4 (36) | 0.12 |
| | Aortic valve n (%) | 9 (50) | 4 (57) | 5 (45) | 1 |
| | Aortic and mitral valves n (%) | 2 (11) | 2 (29) | 0 | 0.14 |
| | Extravalvular extension n (%) | 6 (33) | 2 (29) | 4 (36) | 1 |
| | Any valve regurgitation > 2+ n (%) | 11 (61) | 4 (57) | 7 (64) | 1 |
| Stroke characteristics | Intracerebral hemorrhage n (%) | 6 (33) | 2 (29) | 4 (36) | 1 |
| | Ischemic stroke n (%) | 7 (39) | 4 (57) | 3 (27) | 0.33 |
| | Cerebral microbleeds n (%) | 4 (22) | 2 (29) | 2 (18) | 1 |
| | Subarachnoid Hemorrhage n (%) | 4 (22) | 0 | 4 (36) | 0.12 |
| IIA characteristics | Anterior circulation location n (%) | 15 (83) | 6 (86) | 9 (82) | 1 |
| | Proximal vessel n (%) | 7 (39) | 3 (43) | 4 (36) | 1 |
| | Saccular morphology n (%)[a] | 7 (39) | 0 | 7 (64) | 0.01 |
| | Fusiform morphology n (%)[a] | 10 (56) | 6 (86) | 4 (36) | |
| | Length or width > 3 mm n (%) | 5 (28) | 3 (43) | 2 (18) | 0.32 |

IQR: interquartile range.
[a] One IIA was dysplastic and was classified as neither saccular or fusiform.

aneurysmal dimensions > 3 mm (p = 0.32) did not associate with unfavorable aneurysmal outcome.

### 3.2. Aneurysms during cardiac valve surgery

Twenty-seven (63%) patients with IIA underwent surgical valve repair (Fig. 1). Seven (26%) had preoperative unsecured aneurysm (Table 2) while twenty (74%) had angiographic confirmation of secured aneurysm before surgery.

In the unsecured group, vessels were left untreated for the following reasons (Supplementary Table 1): two unresolved for high risk of vessel sacrifice, two unresolved with clinical instability and need for urgent valve repair, one for inaccessible location, and one was left untreated due to small aneurysm size. Median time from angiogram to valve surgery in the unsecured aneurysm group was 7 days (IQR 2–8) and 5.5 days (IQR 3–9) in the secured group (p = 0.74). No patients in either cohort had perioperative SAH or aneurysmal rupture. Perioperative hemorrhagic transformation of subacute ischemic infarction was observed in one patient in each group.

**Table 2**
Neurologic outcomes after surgical valve repair.

| | Total | Unsecured IIA | Secured IIA | P-Value |
|---|---|---|---|---|
| | n = 27 | n = 7 | n = 20 | |
| Pre-surgical characteristics | | | | |
| Age, median (IQR) | 46 (32–56) | 47 (33–53) | 45 (35–57) | 0.83 |
| Interval from IIA discovery to valve surgery, median days (IQR) | 8 (3–8) | 7 (2–8) | 5.5 (3–9) | 0.74 |
| Antibiotic duration to time of valve surgery, median days (IQR) | 14 (8–35) | 13 (8–18) | 22 (9–46) | 0.26 |
| Male (%) | 22 (81) | 7 (100) | 15 (75) | 0.28 |
| Caucasian (%) | 20 (74) | 6 (86) | 14 (70) | 0.63 |
| Coronary artery disease (%) | 5 (19) | 0 | 5 (25) | 0.28 |
| Hypertension (%) | 11 (41) | 3 (43) | 8 (40) | 1.0 |
| Diabetes mellitus (%) | 2 (7) | 2 (26) | 0 | 0.06 |
| Hyperlipidemia (%) | 9 (33) | 3 (43) | 6 (30) | 0.65 |
| Ischemic stroke at presentation (%) | 21 (78) | 5 (71) | 16 (80) | 0.63 |
| Intracranial hemorrhage at presentation (%) | 2 (7.4) | 0 | 2 (10) | 1.0 |
| Aortic valve repair (%) | 15 (56) | 4 (57) | 11 (55) | 1.0 |
| Aortic and mitral valve repair (%) | 4 (14) | 1 (14) | 3 (15) | 1.0 |
| Extravalvular extension of IE (%) | 11 (41) | 3 (43) | 8 (40) | 1.0 |
| Perioperative complications (7 days post-surgery) | | | | |
| Hemorrhagic expansion of pre-operative Ischemic Infarction (%) | 1 (4) | 1 (14) | 1 (5) | 0.46 |
| Expansion of a pre-operative intracranial hemorrhage (%) | 0 | – | 0 | – |

IQR: interquartile range.

## 4. Discussion

Our cohort of 25 aneurysms demonstrated favorable aneurysmal outcome in seven patients of resolution or regression during mean antibiotic duration of 36 days. Favorable aneurysmal outcome represented only 28% of all aneurysms meeting inclusion criteria for study, or 39% of all aneurysms with follow up angiography. Unfavorable outcomes occurred in 44%, with only 1 rupture (4%) but 24% with enlargement and 8% with new aneurysm. Overall, this suggests that even with extended antibiotic dosing, IIA response to antibiotics is of limited efficacy. A systematic review similarly found variable responses of aneurysms to antibiotic treatment [1]. Our result differs slightly from a prior study in which 7 out of 16 (44%) aneurysms showed regression/resolution (favorable outcome) [7]. In a smaller cohort, 4/7 (57%) had favorable IIA outcome with antibiotic treatment [8]. Another study consisting of 18 patients demonstrated similar results to ours as 6/18 (33%) patients had favorable IIA outcomes [9]. Overall, 28–57% of IIA appear to resolve or decrease in size, and 10–32% may develop new IIA or grow [7–9]. It is important to note that duration of antibiotic treatment and definitions of outcomes varied across these prior studies. In our cohort, interval follow up between aneurysms with unfavorable outcomes was tended to be shorter than those with favorable outcomes ($p = 0.06$). The study also demonstrates the dynamic course of mycotic aneurysms (Supplementary Figure). Only 2 patients with interval angiographic follow up had no change of the aneurysm. In a followup interval of median 21 days, 11 patients had unfavorable aneurysmal outcomes. There were two patients in the cohort with initial negative DSA, each of which had repeat angiogram within 48 h with one growth and subsequent rupture, and one with growth without rupture.

We found that all seven mycotic aneurysms with saccular morphology receiving follow up angiography had unfavorable outcomes (4 enlargement, 1 new IIA, 2 no change). However, the only aneurysmal rupture seen in our cohort after initial discovery of IIA was in a fusiform IIA. Also, aneurysmal growth in non-mycotic aneurysms is a known risk factor for rupture, making a relatively rapidly evolving IIA theoretically higher risk for rupture [10]. Given our cohort demonstrated that saccular morphology is associated with these defined unfavorable outcomes, this suggests these aneurysms may need to be treated more aggressively than with antibiotics alone. Our finding should be replicated in a larger cohort study.

While morphology was predictive of IIA outcome, other intrinsic IIA characteristics such as size and location were not related to outcome (Table 1). It has been shown that presence of hemorrhages and microhemorrages at presentation are predictive of the presence of IIA [11–14]. However, while hemorrhages at presentation may predict presence of IIA, our cohort did not find presence of subarachnoid hemorrhage or intracranial hemorrhage to be predictive of aneurysmal outcome (Table 1).

We observed that a relationship between antibiotic duration prior to aneurysm discovery and regression or resolution with antibiotic treatment. Patients with IIA with subsequent regression or resolution had median antibiotic pre-treatment of 9 days, compared to unfavorable aneurysmal outcome with median antibiotic treatment of only one day at time of IIA discovery (Supplementary Figure). The only aneurysm rupture observed in our cohort occurred after five days of antibiotic treatment. We hypothesize that aneurysms found early in their course may be at higher risk for unfavorable outcome as they have had less duration of antibiotic exposure. Unruptured aneurysms found during longer exposure to antibiotics might be stable, portending a better outcome.

Seven patients with an identified unsecured IIA underwent surgery with full dose intraoperative heparin during cardiopulmonary bypass. There were no aneurysmal ruptures seen in this group, and no aneurysmal ruptures seen in the entire surgical cohort of 27 patients. While the median time to valve surgery in the unsecured aneurysm group was 7 days, it is reasonable to assume the unsecured IIA had not spontaneously resolved prior to surgery with antibiotic treatment alone. It has been hypothesized the perioperative rupture rate is likely higher for mycotic aneurysm since IIA are typically thin-walled and friable, and often with a wide or absent neck than a typical aneurysm [1,15]. In small case series of patients, a subgroup of 3 patients had unclipped IIAs prior to valve surgery, with no perioperative aneurysmal ruptures [16]. This is similar to what was observed in our study. Though a small cohort, our observation suggests that the perioperative risk of rupture may not be high. Prior studies involving operative outcomes predominantly focus on patients with preoperative ischemic strokes, preoperative intracranial hemorrhages, or preoperative SAH.

Our study has a single center retrospective design with a small sample size. Given the rarity of IIA, this may represent the largest single center series of mycotic aneurysms. Multiple aneurysmal outcomes were grouped together for final analysis, which may limit interpretation. The follow up angiographic images only gives snapshots of aneurysms, and we cannot exclude the possibility of growth followed by regression and vice-versa. There were also seven patients had no follow up angiogram, and final aneurysmal outcome could not be verified in this group. No subsequent clinical subarachnoid hemorrhage observed among these patients. Given the retrospective nature of the study, timing of interval angiography, duration of antibiotic treatment, antibiotic choice, and timing of surgery could not be controlled for.

## 5. Conclusion

Antibiotics treatment alone led to resolution in 28% of confirmed mycotic aneurysms. Patients undergoing longer antibiotic therapy prior to discovery of unruptured IIA may have increased chance of improved aneurysmal outcome, while saccular morphology may correlate with unfavorable aneurysmal outcome. The risk of perioperative rupture of unsecured IIA may not be high.

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B.) Competing Interest Statement: Authors declare no competing interests.

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D.) Data Sharing: Data will be made available upon request.

## Declarations of interest

None.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.06.004.

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