

## A dangerous dilemma: management of infectious intracranial aneurysms complicating endocarditis

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A 41-year-old right-handed man with bicuspid aortic valve and a 3-month history of chronic fever and weight loss presented with sudden onset of severe headache. Computerised tomography of the head revealed a right basal ganglia haemorrhage. Further investigation documented *Streptococcus mitis* bacteraemia, a fusiform right middle cerebral artery aneurysm, and an abscess at the base of the anterior leaflet of the mitral valve. The patient subsequently died when repeat aneurysmal haemorrhage resulted in cerebral herniation and brain death while on antibiotic therapy. Infectious intracranial aneurysms (IIAs) are uncommon but severe complications of bacterial endocarditis. Several case series have been published evaluating the management of IIAs, but no randomised controlled trials exist to guide treatment decisions. Improved diagnostic techniques, microvascular neurosurgical approaches, and endovascular therapies hold the promise of improved outcomes in the future. This difficult case is used to show an approach towards the management of IIAs complicating bacterial endocarditis based on a review of the published work.

### Case presentation

A 41-year-old right-handed man from Colombia, South America, presented to the emergency room with the sudden onset of the worst headache of his life. He complained of an intense throbbing headache localising to the right temple. On further questioning he reported not feeling well for the previous 3 months and described intermittent fever, fatigue, and 10 kg weight loss. He had no known history of medical problems and he had moved to the USA 4 years previously.

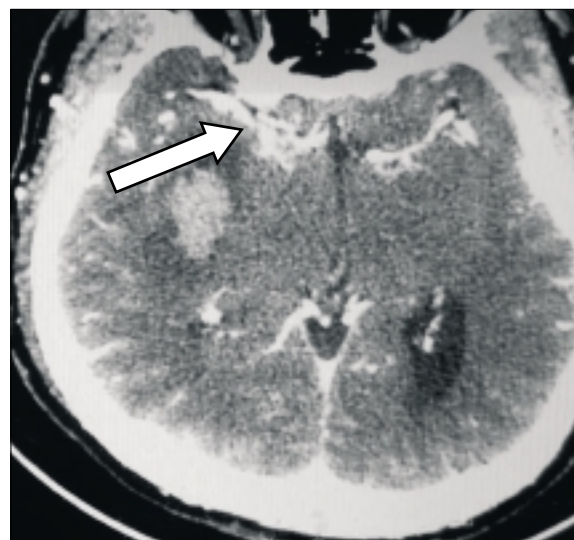
On physical examination he had a temperature of 38.0°C, heart rate of 70 beats per min, and blood pressure of 125 per 74 mm Hg. He was breathing 16 breaths per min and saturating at 98% on room air. He appeared fatigued but not acutely ill. He had good dentition, a supple neck, and fundoscopic examination revealed no lesions. Neurological examination was notable for a mild left hemiparesis with normal mentation, cranial nerve function, sensation, and reflexes.

His complete blood count, extended metabolic panel, and coagulation studies were unremarkable. Chest radiograph was normal and his electrocardiogram showed a normal sinus rhythm with normal conduction intervals. Computed tomography (CT) of the head without contrast showed a 1.1 cm right external capsule/basal ganglia haemorrhage with surrounding oedema and mild local mass effect but no mid-line shift. There was also evidence of adjacent subarachnoid haemorrhage.

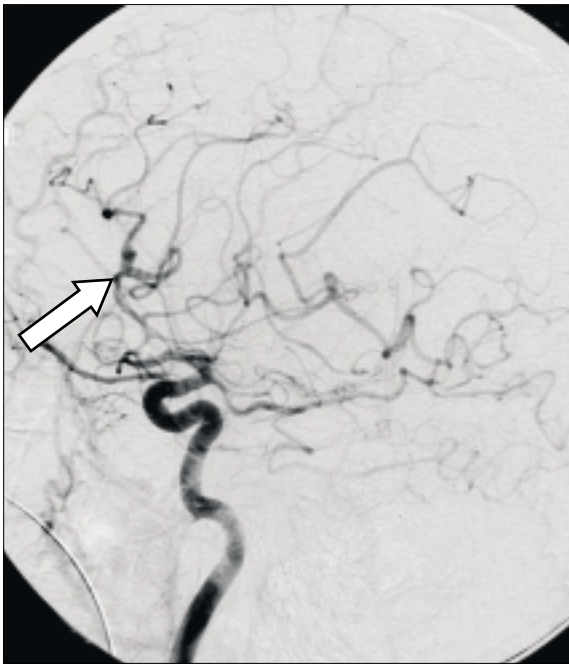
He was admitted to the hospital for further evaluation and management of his intracerebral and subarachnoid haemorrhage. Soon after he experienced a precipitous decline in neurological status and became only responsive to pain. He stopped spontaneously moving his left side, with associated hyperreflexia and a positive Babinski sign on the left. Repeat CT scan showed extensive increased right subcortical haemorrhage with effacement of the sulci and ventricles, and local mass effect. Helical CT angiogram showed a diffuse enlargement of the right middle cerebral artery (MCA) along its course through

the sylvian fissure (figure 1). Digital subtraction angiography confirmed the presence of a fusiform aneurysm with surrounding vasospasm at the bifurcation of the M2 branch of the right MCA (figure 2). Blood cultures drawn at the time of admission became positive for *Streptococcus mitis* (intermediate sensitivity to penicillin, sensitive to ceftriaxone) and the patient was started on ceftriaxone 2 g intravenously twice daily and gentamicin 75 mg intravenously three times daily. A transoesophageal echocardiogram showed an abscess at the base of the anterior leaflet of the mitral valve with a perforation of its leaflet that tracked to the left cusp of a bicuspid aortic valve. There was evidence for perivalvular leak at the mitral valve and otherwise a left ventricular ejection fraction of 55%.

Emergent neurosurgical evaluation showed the patient to be a poor neurosurgical candidate in view of the intracranial aneurysm's extensive course, proximal



**Figure 1: Computed tomographic angiogram**  
Diffuse enlargement of the right middle cerebral artery along its course through the sylvian fissure and associated intracranial haemorrhage.



**Figure 2: Digital subtraction angiogram**  
Fusiform aneurysm with surrounding vasospasm at the bifurcation of the M2 branch of the right middle cerebral artery.

location, and fusiform anatomy. He remained haemodynamically stable on intravenous antibiotics and subsequent sets of blood cultures had no growth. His mental status improved but his dense left hemiparesis persisted. Repeat CT scan revealed no interval changes. A decision was made to continue antibiotic therapy and repeat the CT angiogram. Unfortunately, on hospital day 22 his aneurysm suddenly ruptured again with ensuing right uncal herniation. The patient's clinical status quickly deteriorated and care was discontinued after he was pronounced brain dead. Subsequent necropsy confirmed a complex aneurysm along the course of the right MCA. Histological examination revealed disruption of the small vessels within the aneurysm by neutrophils (figure 3). Gram stain revealed no evidence of bacteria in the aneurysm.

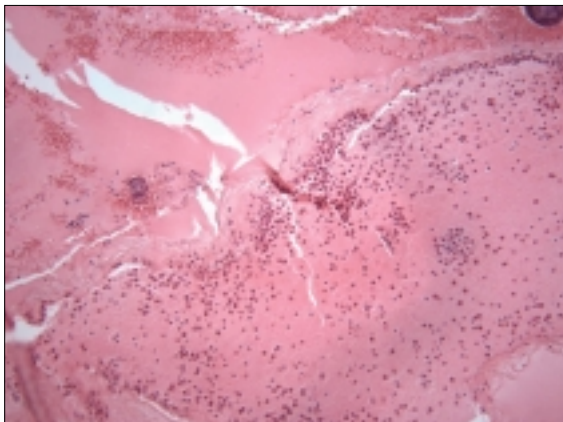
### Review and discussion

Osler<sup>1-3</sup> first described a patient with sub-acute bacterial endocarditis who at autopsy had a ruptured aortic aneurysm secondary to "mycotic endarteritis". Church<sup>4</sup> had previously described a ruptured middle cerebral artery aneurysm in a boy with mitral valve endocarditis. At the turn of the 19th century, "mycotic" was used to describe all microorganisms, and mycotic aneurysm was coined to describe any aneurysm resulting from infection. Mycotic is now reserved for fungal infections, although the term mycotic aneurysm has persisted in the endocarditis literature. Recently, the more accurate term infectious aneurysm has supplanted mycotic aneurysm in the neurosurgical literature.<sup>5</sup>

### Epidemiology

Infectious aneurysms have typically developed in the presence of bacterial endocarditis. A pre-antibiotic-era case series showed that 86% of all infectious aneurysms were associated with bacterial endocarditis and the majority were located in the aorta.<sup>6</sup> The advent of antibiotics and increased prevalence of atherosclerotic disease has shifted the epidemiology so that bacterial seeding of atherosclerotic vessels<sup>7,8</sup> and sites of arterial trauma<sup>9,10</sup> now cause most extracranial infectious aneurysms in developed countries. Infectious intracranial aneurysms (IIAs), however, continue to almost exclusively result from left-sided bacterial endocarditis.<sup>5,11-15</sup> These observations suggest that infected emboli are important for the formation of IIAs.<sup>16</sup> Less frequently, IIAs result from intracranial bacterial infections such as meningitis, cavernous thrombophlebitis, and post-neurosurgical infections.<sup>11,15</sup> These infections can spread from a contiguous focus to invade adjacent arterial walls and cause aneurysmal formation.<sup>11</sup>

Although the epidemiology of endocarditis in developed countries has changed profoundly, the incidence of bacterial endocarditis has remained stable at two to six cases per 100 000 people per year. Risk factors such as prosthetic valves, elderly sclerotic valve disease, nosocomially acquired bloodstream infections, and intravenous drug use have replaced traditional risk factors such as rheumatic heart disease.<sup>17</sup> Neurological complications are still frequent, occurring in up to 30% of infectious endocarditis patients, with stroke complicating 12% of endocarditis cases.<sup>16,18</sup> IIAs are less common (2-4% of endocarditis cases) but produce potentially devastating neurological complications such as intracerebral or subarachnoid haemorrhage.<sup>19-23</sup> Since IIAs can be clinically silent and have been documented to resolve completely on antibiotic therapy, the true incidence of IIAs is probably higher than the 2-4% reported in the literature.<sup>24,25</sup> Intracranial bleeding in the setting of infectious endocarditis is not always secondary to ruptured aneurysms; it is more often caused by simple necrotic arteritis.<sup>26</sup>



**Figure 3: Extensive inflammation and neutrophil infiltration of an aneurysmal vessel wall (Giemsa stain)**

### Microbiology

Viridans group streptococci and *Staphylococcus aureus* are responsible for 57–91% of IIAs. Coagulase-negative staphylococci, enterococci, and beta-haemolytic streptococci are other etiological agents. HACEK (*Haemophilus* spp, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* spp) organisms, Gram-negative rods, and fungi are less commonly reported to cause intracranial aneurysms.<sup>11,19,24,27–31</sup> The microbiology of IIAs in intravenous drug users has not been well described but *S aureus*, the predominant cause of endocarditis in this population,<sup>17</sup> is presumed to be the most important pathogen. Whether *S aureus* or viridans group streptococci have more of a predilection to cause aneurysms is a subject of debate. *S aureus* does cause higher overall rates of neurological complications.<sup>32</sup> However, a study comparing endocarditis with and without IIAs did not show any microbiological associations.<sup>33</sup>

### Pathophysiology

IIAs arise from either septic microemboli to the vasa vasorum or occur secondary to bacterial escape from a septic embolus that has occluded a vessel.<sup>5,8</sup> In a dog model of septic emboli, bacteria delivered to the internal surface of the vessel caused acute inflammation in the adventitia, with internal spread through the muscularis layer resulting in disruption of both the internal elastic membrane and intima.<sup>34</sup> Because of the involvement of the muscular layer, infectious aneurysms are actually pseudo-aneurysms. Within the central nervous system IIAs can form anywhere, but have a striking predilection for the distal branching points of the middle cerebral artery. This location contrasts with congenital aneurysms which tend to be central.<sup>32</sup> In a review of angiographically proven IIAs, 55/71 (77%) aneurysms occurred in the distal middle cerebral artery.<sup>35</sup> Multiple aneurysms are demonstrated in up to 25% of cases.<sup>12–14,24,25</sup>

### Diagnosis

Most patients with endocarditis who develop aneurysms have a history of systemic symptoms (malaise, fever,

weight loss) that precede the onset of a neurological event.<sup>33</sup> Although septic embolisation precedes aneurysmal formation, these events are often clinically silent. Nevertheless, in some clinical series a focal neurological deficit indicating an embolic infarction is the most common prodrome.<sup>21,32</sup> Severe, localising headache in a patient with infective endocarditis can also indicate the presence of an IIA.<sup>16,32</sup> Occasionally, patients have confusion, meningitis, or seizures secondary to herald leaks. Local compression from an expanding aneurysm can also cause cranial nerve palsy.<sup>32</sup> Unfortunately these neurological symptoms also frequently occur in patients with endocarditis who never develop aneurysms. An uncontrolled comparison of patients with endocarditis showed no significant differences in neurological symptoms to distinguish patients who developed aneurysms.<sup>33</sup> In the context of these diagnostic difficulties, many IIAs are not suspected until rupture occurs. Therefore any neurological symptom should raise the suspicion for an intracranial aneurysm and lead to further diagnostic evaluation.

CT scanning is the most useful initial test to evaluate a patient with endocarditis and neurological symptoms, particularly when intracranial or subarachnoid haemorrhage is suspected. CT is a sensitive method for detecting intracranial blood and may additionally show evidence of abscess, hydrocephalus, or infarction. Aneurysms can even be visualised with helical CT angiogram. In a case series of 34 patients with endocarditis and neurological symptoms who all underwent head CT and angiogram, all 14 patients with a normal head CT had a normal angiogram and 55% of patients with an abnormal head CT had evidence of an aneurysm on angiogram.<sup>36</sup> Other reports, however, demonstrate that a normal head CT does not rule out an IIA and angiography is required if there is a high clinical suspicion.<sup>30</sup> Magnetic resonance angiography is an additional powerful tool to non-invasively visualise intracranial aneurysms with a sensitivity approaching four-vessel angiogram for non-infectious intracranial

Study*	Institution	Time period	Antibiotic therapy only (deaths/total patients)	Combined therapy (deaths/total patients)
Ojemann <sup>5</sup>	Various	1959–78	0/7	0/2
Frazer et al <sup>19</sup>	University of California, Los Angeles, (UCLA), Los Angeles, CA	1955–78	0/1	0/1
Brust et al <sup>30</sup>	Harlem and St. Luke's-Roosevelt Hospitals, New York, NY	1969–87	1/3	0/4
Aspoas and de Villiers <sup>31</sup>	Groote Schuur Hospital, Cape Town, South Africa	1971–90	1/4	0/5
Phuong et al <sup>13</sup>	Mayo Clinic, Rochester, MN	1976–99	2/2	0/2
Ahmadi et al <sup>15</sup>	University of Southern California (USC), Los Angeles, CA	1980s	0/1	0/1
Corr et al <sup>24</sup>	Groote Schuur Hospital, Cape Town, South Africa	1983–92	0/4	0/1
Chun et al <sup>12</sup>	University of California, San Francisco (UCSF), San Francisco, CA	1990–2000	0/3	0/2

\* Only the results for patients with unruptured aneurysms in each of these case series are included in this table.

**Table 1: Comparison of mortality in patients with unruptured infectious intracranial aneurysms treated with either antibiotics alone, or combined surgery and antibiotics**

aneurysms.<sup>37</sup> Currently, traditional four-vessel angiogram remains the gold standard for infectious aneurysms because of their propensity for distal and atypical locations.

### Treatment

Treatment of IIAs remains a controversial topic lacking randomised controlled trials to guide clinical decision making. There is an abundance of anecdotal reports showing both striking successes and failures of either conservative antibiotic therapy alone, or combined antimicrobial and surgical therapy. Fortunately, the advent of noninvasive imaging modalities and minimally invasive interventional techniques have provided more diagnostic and therapeutic options. Modern case series report lower rates of mortality than observed historically.<sup>5,12,14</sup> Decisions regarding the most appropriate therapy must be individualised based on input from experienced neurosurgeons, interventional neuroradiologists, and neurologists.

When considering treatment, the most important factor is whether the aneurysm has ruptured. Table 1 summarises several case series reporting mortality with unruptured IIAs stratified by treatment. Physicians will increasingly encounter this problem as improved imaging techniques visualise more asymptomatic unruptured aneurysms. These case series are single-centre experiences and treatment decisions were not controlled. Another limitation is that only mortality is considered, since long-term morbidity is difficult to standardise and often not reported. Mortality rates were low in both groups and the majority of patients without rupture never required neurosurgery. Furthermore, several case series have documented resolution of IIAs up to 10 mm in diameter with medical therapy alone.<sup>25,38–40</sup>

Unruptured aneurysms should, therefore, receive antibiotic therapy with serial angiography to document improvement or resolution. If the aneurysm is very large, not resolving, or enlarging despite antibiotics, the patient will require surgery or endovascular therapy. One case series evaluated this management strategy in 14 patients with both ruptured and unruptured IIAs. Of the five patients with unruptured aneurysms, four resolved completely on antibiotics, one aneurysm decreased in size but ultimately required surgical excision, and none ruptured. Of the remaining nine patients with ruptured aneurysms only one completely resolved on antibiotics, one patient died before surgery, and the remaining seven patients required surgical excision for persistent aneurysms.<sup>24</sup>

Ruptured aneurysms have a worse prognosis. Table 2 summarises several case series reporting mortality with ruptured IIAs, again stratified by treatment. Patients treated with combined surgery and antibiotics had a better prognosis than with antibiotics alone. This uncontrolled data is, of course, subject to bias. Patients who did not undergo surgery (like our patient) may have been judged to be too sick to tolerate surgery or may have died while awaiting a planned surgery, which would bias the data in favour of surgery. Most case reports are published in the neurosurgical literature, which may bias towards publishing positive surgical results. Conversely, patients who underwent heroic emergency surgery with little chance for survival might have biased the data against surgery. Regardless, in view of the poor outcomes with antibiotic therapy alone, strong consideration should be given to surgery if the aneurysm has ruptured. More difficult situations arise when the aneurysm is proximal and supplying large areas of eloquent neural territory and care must be individualised based on experienced

Study*	Institution	Time period	Antibiotic therapy only (deaths/total patients)	Combined therapy (deaths/total patients)
Ojemann <sup>5</sup>	Various	1959–78	8/14	7/24
Frazer et al <sup>19</sup>	University of California, Los Angeles, (UCLA), Los Angeles, CA	1955–78	6/7	0/4
Brust et al <sup>30</sup>	Harlem and St Luke's-Roosevelt Hospitals, New York, NY	1969–87	1/2	2/8
Bullock et al <sup>27</sup>	Durban and Bloemfontein, South Africa	1970s	4/4	1/5
Aspoas and de Villiers <sup>31</sup>	Groote Schuur Hospital, Cape Town, South Africa	1971–90	0/1	1/15†
Phuong et al <sup>13</sup>	Mayo Clinic, Rochester, MN	1976–99	1/4	0/8
Monsuez et al <sup>29</sup>	Hospital Saint-Louis, Paris, France	1978–85	2/6	1/6
Barrow and Prats <sup>21</sup>	Emory University, Atlanta, GA	1980s	0/2	0/4
Ahmadi et al <sup>25</sup>	University of Southern California (USC), Los Angeles, CA	1980s	0/0	0/3
Corr et al <sup>24</sup>	Groote Schuur Hospital, Cape Town, South Africa	1983–92	1/1	0/8
Venkatesh et al <sup>28</sup>	Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India	1989–99	2/10	0/7
Chun et al <sup>12</sup>	University of California, San Francisco (UCSF), San Francisco, CA	1990–2000	1/2	1/13

\*Only the results for patients with ruptured aneurysms in each of these case series are included in this table. †One patient with unknown outcome was presumed dead.

**Table 2: Comparison of mortality in patients with ruptured infectious intracranial aneurysms treated with either antibiotics alone, or combined surgery and antibiotics**

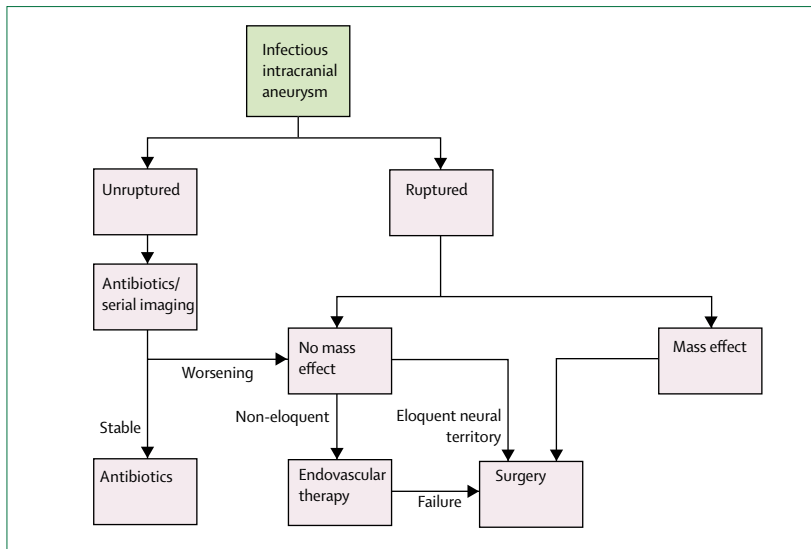


Figure 4: Management algorithm for infectious intracranial aneurysm based on expert opinion<sup>12-14,16,24,47</sup>

neurosurgical input. The timing of surgery is also complicated. Infected aneurysms are often quite friable, surgically difficult to clip, and may require excision.<sup>12</sup> Contingent upon the morphology and location of the aneurysm, the surgeon might elect to excise, ligate, clip, or wrap the affected vessel. Artery-to-artery bypass, if technically feasible, could preserve neuronal tissue in an affected vessels' vascular distribution. Some neurosurgeons advocate delaying definitive surgical therapy, if possible, until antibiotics have been given. Unfortunately there is no way to determine if an aneurysm is at imminent risk of catastrophic haemorrhage. In a case series involving nine patients who developed subarachnoid haemorrhage secondary to an aneurysm while on antibiotics for bacterial endocarditis, the median time to bleed was 23 days with a range of 5 to 35 days.<sup>19</sup>

Endovascular therapy has been an exciting advance for the treatment of IIAs. Endovascular technology can occlude an aneurysm with little manipulation or risk of rupture, though typically with sacrifice of the parent vessel. A case series of 14 patients with bacterial endocarditis reported the treatment of 18 IIAs with endovascular therapy using nonselective cyanoacrylate occlusion or coil occlusion.<sup>14</sup> Ruptured, unruptured, proximal, and distal aneurysms were represented in the study. All aneurysms were successfully occluded, there were no aneurysmal ruptures, there were no deaths, and only two patients had transient procedure-induced neurological defects. The authors attribute their low rate of neurological complications to two factors. First, since infectious aneurysms often develop secondary to a septic embolus (which can be clinically silent), the damage might have already occurred before endovascular vessel occlusion. Second, endovascular techniques can use selective amobarbital injection in a conscious patient to

establish whether the aneurysmal artery is still perfusing eloquent neural tissue. Another review of 16 patients with IIAs (88% ruptured) who were treated with endovascular therapy confirmed its safety and efficacy.<sup>12</sup> Endovascular occlusion was successful in 88% of cases. Complications included treatment-induced neurological sequelae in two patients and two deaths (unrelated to endovascular therapy). The major limitation of endovascular therapy for ruptured aneurysms not addressed in these case series is its inability to deal with an adjacent haematoma. A resulting haematoma may cause raised intracranial pressure and mass effect that can only be decompressed surgically. A theoretical risk of foreign material infection and abscess formation also exists<sup>41</sup> but was not seen in either study.<sup>12,14</sup> Additionally, five patients were reported as able to undergo cardiac surgery within 1 week of endovascular therapy with no bleeding complications.<sup>14</sup>

Microvascular neurosurgical techniques have also improved and are particularly important in the treatment of IIAs involving arteries that supply eloquent neural tissue. Surgical techniques can preserve vascular flow, which offers a distinct advantage over endovascular therapy. Typically a segment of the artery will be excised with the IIA to ensure healthy uninvolved arterial vessel margins. Many IIAs are small, which permits resection and primary end-to-end reanastomosis.<sup>12</sup> Larger aneurysms can be trapped and bypassed. Bypass options include the superficial temporal artery,<sup>42</sup> a sylvian artery, or a saphenous vein graft.<sup>43</sup>

Multiple IIAs (which occur in 25% of cases) complicate treatment, although the same therapeutic principles apply. Management should be dictated by the most dangerous aneurysm. Multiple unruptured aneurysms can be treated with antibiotic therapy alone and serial angiography. If both ruptured and unruptured aneurysms are present, management should be dictated by the ruptured aneurysm with an immediate neurosurgical evaluation for definitive neurosurgical or endovascular therapy. Patients with multiple IIAs have not had worse clinical outcomes compared with patients with single IIAs in several case series.<sup>12-14,24,25,35</sup>

Cardiac surgery is not usually recommended in the setting of an acute aneurysmal rupture. A review of patients with endocarditis and an acute neurological event who required cardiac surgery included three ruptured and four unruptured aneurysms.<sup>44</sup> The three patients with ruptured aneurysms all had craniotomy with aneurysm clipping before cardiac surgery. One patient died after undergoing cardiac surgery 2 days after craniotomy. The other two patients were cardiovascularly stable and waited 21 and 35 days respectively before cardiac surgery with good outcomes. None of the four unruptured aneurysms were clipped and all of the patients had good cardiac surgical outcomes. The authors recommended a 2 to 3 week waiting period on antibiotics after craniotomy for a ruptured aneurysm before

### Search strategy and selection criteria

Data for this review were identified by searches of PubMed. Search terms included "intracranial mycotic aneurysm", "infected aneurysm", "infectious intracranial aneurysm", "endocarditis", "subacute bacterial endocarditis", "therapeutic embolization", and "ruptured aneurysm". We also reviewed references to identify additional published literature, including some articles that predated the earliest available on Medline. Non-English language papers were also considered.

undergoing cardiac surgery and a conservative approach with unruptured aneurysms.<sup>44</sup> There are case reports, however, of unruptured IIAs rupturing after cardiac surgery.<sup>45</sup> There is also a growing body of evidence that patients with ruptured aneurysms treated endovascularly can undergo cardiac surgery after a shorter waiting period.<sup>14,46</sup>

We propose a management algorithm (figure 4) for IIAs based on expert opinion.<sup>12–14,16,24,47</sup> Appropriate antibiotic therapy should be initiated in all patients according to the same principles recommended for infectious endocarditis. Supportive measures such as blood pressure management and avoidance of unnecessary anticoagulation should be instituted. The most important branch in the algorithm is whether the aneurysm has ruptured. Many unruptured aneurysms will resolve with antibiotic therapy. These aneurysms should be followed closely with serial imaging using the least invasive test that can visualise the aneurysm. Although the exact timing of serial imaging is not known, intervals of 7 to 14 days have been recommended.<sup>16</sup> Aneurysms that rupture, enlarge, or persist should be evaluated for endovascular or neurosurgical intervention. Ruptured aneurysms require immediate neurosurgical attention if the haematoma is causing mass effect and raised intracranial pressure. Ruptured aneurysms that do not require emergency surgery should be evaluated for endovascular therapy. Selective amobarbital testing can determine if occluding the aneurysm will infarct additional eloquent neural tissue. If the residual neural tissue is eloquent, microvascular neurosurgical techniques have the best success at preserving vessel patency.<sup>12</sup>

### Conclusions

IIAs will continue to be a rare but devastating neurological complication of infectious endocarditis. Although diagnostic and therapeutic techniques have improved, the management of these aneurysms is complicated by the absence of randomised controlled trials. There is clearly a need for prospective research into the natural history of and optimal treatment for IIAs. In view of the rarity of this clinical condition, large prospective cohort studies such as the International Collaboration on Endocarditis<sup>48</sup> provide the best forum to evaluate treatment strategies and outcomes in this ancient, dangerous disease.

### Conflicts of interest

We declare that we have no conflicts of interest.

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