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Acute Management of Brain Arteriovenous Malformations

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Opinion statement

Major reasons to treat brain arteriovenous malformations (AVMs) are to reduce the risk of brain hemorrhage, control intractable seizure, and in some cases alleviate neurologic deficits. Once an AVM has hemorrhaged, the risk of further hemorrhage is increased and it should be treated. The treatment plan ideally is based on interdisciplinary discussion between neurosurgery, endovascular neuroradiology, and radiotherapy, moderated by neurology in an experienced center. Complete removal or obliteration of the malformation should be the goal, as partial treatment only exposes the patient to treatment risks with a residual hemorrhage risk. If an AVM is surgically accessible with acceptable treatment risk, neurosurgical removal leads to the fastest and most complete reduction of hemorrhage risk. Radiotherapy is best used in small AVMs with contraindications to surgery. Endovascular embolization can be used as an adjunct for both to facilitate removal or obliteration or to reduce risks from associated aneurysms or high-flow fistulae, and may in some cases lead to complete occlusion. Unbled AVMs require a thorough assessment of projected hemorrhage risk versus treatment risks, as the natural course is influenced by clinical and morphological factors. Given recent scientific evidence, those with low projected hemorrhage risks should be managed conservatively, receiving the best medical treatment of accompanying symptoms, and careful clinical and follow-up imaging monitoring. Thorough and objective counselling of the patients about pros and contras of therapy, detailed explanation of recommendations, and possible reevaluation of treatment decisions at later timepoints are recommended.

Introduction

The most general definition of brain arteriovenous malformations (AVMs) is that they are comprised of a more or less complex nidus fed by one or more arteries, draining into one or more veins under circumvention of

the capillary bed. It has long been assumed that there is no normal functional brain tissue in the nidus [1, 2], a view which is under current challenge [3]. AVMs come in a variety of anatomic features. Feeders can be single or multiple; they can originate from arteries of the proximal Circle of Willis or from the hemispheral surface or the distal arterial borderzone arteries that are formed during late fetal life [1, 4]. The nidus proper can be small and sharply defined, but also large or with diffuse margins [5], making difficult surgical efforts to separate the AVM from healthy brain tissue. The venous drainage can be single or multiple, exclusively to the superficial venous system or participating in the deep venous drainage of the brain, the latter repeatedly described as increasing hemorrhage risk [4, 6]. Venous stenosis and aneurysmal ectasia are common findings with suspected but non-proven increased risk of hemorrhage in the natural history risk [7]. Further variations regarding AVM development over time or presenting symptoms at different age groups make AVMs difficult to evaluate as a single entity [8–10]. Accordingly, therapeutic approaches must be specifically tailored based on the balance between best estimates of the natural course risk and the individual treatment plan.

There are only few data available from population-based studies on the natural course risk of AVMs, and much information stems from single- or multicentre datasets [11–15]. The majority of AVMs are discovered incidentally by the increasing availability of modern brain imaging [8, 11, 16, 17]. If AVMs present clinically, it is with hemorrhage or seizures in the majority of patients. Less frequently, headaches or neurologic deficits caused by displacement of brain structures or venous outflow obstruction may also lead to the diagnosis [1, 18, 19•, 20–22].

Brain hemorrhage, the most feared clinical presentation, was found to be associated with prior hemorrhage, deep AVM location, exclusive deep venous drainage, and increasing age [4, 23, 24••, 25]. The annual hemorrhage risk ranges from below 1 % to over 30 %, depending on the presence of each of these risk factors [4], with prior hemorrhage being the strongest predictor of further bleeding [4, 11, 26, 27]. Small AVM size, concomitant aneurysms, and genetic factors have also been described as risk factors [7, 28–30]. It remains unclear whether the risk of AVM hemorrhage is a lifetime constant or if it changes over time. The best possible determination of the individual hemorrhage risk is an important step towards a treatment decision. Because of the risk of early recurrence, current practice is for AVMs that have hemorrhaged to undergo complete removal with the least therapeutic risk; by contrast, unbled AVMs carry a lower natural course risk, the hemorrhage that usually occurs being better characterized as a leak rather than a rupture, often a minor clinical event, and therefore requires careful evaluation if interventional treatment is to be considered at all [31–33]. Recent publications showed an excess risk of stroke and impairment for patients with interventional treatment for unbled AVM considered suitable for attempted removal [34••, 35••] (Fig. 1), which generated much discussion worldwide about the need for interventional treatment of unbled AVMs [36, 37].

Treatment options include surgical removal, endovascular embolization, stereotactic radiotherapy, a combined therapeutic approach, or the conservative management directed at medical symptomatic treatment [38••, 39, 40•, 41]. Therapeutic decisions should be made in an interdisciplinary team [42, 43] with all options available and are discussed below.

Treatment

AVM hemorrhage

Diagnosis

- The majority of AVMs are diagnosed without having suffered hemorrhage. Roughly 2.5 times more AVMs are diagnosed with an unruptured malformation compared with those detected after intracranial bleeding (61 versus 39 % in the New York Islands Study) [44]. There is an ongoing debate on when a diagnosis of an AVM-related

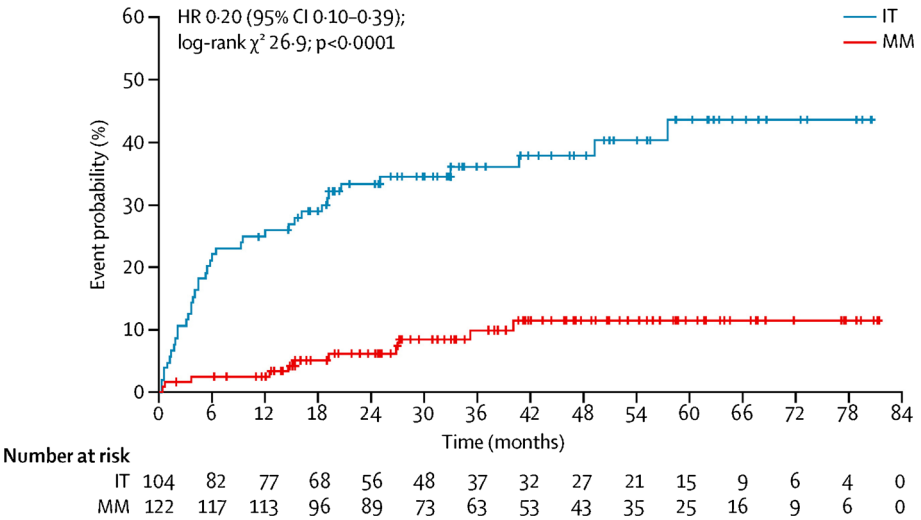

Fig. 1. Kaplan-Meier estimated primary event rate (death or symptomatic stroke) as treated in the ARUBA trial. Mean follow-up 42.8 months (SD 20.5). *IT* interventional treatment and medical management, *MM* medical management alone. From: Lancet 2014;383(9929): 1636

hemorrhage should be diagnosed, given the high hemosiderin sensitivity of modern MRI techniques [45]. Symptomatic hemorrhages can be caused by venous occlusion, or arterial or intranidal rupture.

Clinical impact

- The clinical impact of an AVM rupture was long believed to be the same as that from hypertensive bleeds or aneurysmal hemorrhages. Although devastating in a few patients, AVM hemorrhages as a group carry a much lower morbidity than those caused by other diseases [30, 46]. Possible explanations include bleeding from venous obstruction without the full arterial pressure, rupture into the nidus without the destruction of functional brain tissue, predominantly intraventricular hemorrhage in some patients, and better functional brain reorganization [30]. Given the high risk of recurrence, patients having suffered AVM hemorrhages are prime candidates for complete removal of the AVM [13, 47].

Timing of treatment

- Patients with life-threatening hematomas and hydrocephalus are treated with emergency surgery. Clot removal is best performed in superficial AVMs in which the anatomy is not obscured by compressive effects of the hematoma. Intraventricular hemorrhage may lead to hemo-/hydrocephalus requiring placement of an intraventricular catheter. In all other cases, the timing of AVM treatment should generally be elective in stable patients [48].

AVM surgery

Effectiveness

- Microsurgical AVM resection is the best-known form of treatment, having the longest history. The goal is the complete removal of the AVM, minimizing the subsequent risk of lesion recurrence and hemorrhage. Only few recurrences or residual dysplastic vessels associated with recurrent hemorrhages have been described [49, 50]. Compared with other treatment modalities, complete obliteration by surgery alone is achieved in 96 % (median, range 0–100 %), with a low post-operative hemorrhage rate of 0.18 per 100 person-years [38••].

AVM classification

- An estimate of the surgical risk was provided by the most commonly used Spetzler-Martin grading system. AVM size, presence of deep venous drainage, and eloquent location of the AVM in the brain classify an AVM into one of 5 grades with the surgical risk increasing from grade 1 to grade 5 [51]. Further modifications of the system took into account the effects of hemorrhagic presentation (lower surgical risk), diffuseness of the AVM nidus (higher risk with diffuse nidus), and presence of deep perforating artery supply (higher surgical risk when present) [52–54]. More recently, a 3-tier classification system was proposed combining original grades 1 and 2 into class A (cases in grade 2 are not simply those with larger AVM but can include those with deep venous drainage or 'eloquent' location—but not both), grade 3 as class B, and grades 4 and 5 into class C AVMs [55]. Following this classification, microsurgical AVM resection is recommended for class A, combination treatment with prior embolization or subsequent radiotherapy for class B, and conservative management for class C AVMs, unless the latter show recurrent hemorrhages, progressive deficits, or intractable seizures [48, 55, 56]. It is noteworthy that these recommendations come from publications which did not segregate those without prior hemorrhage from those who have bled, and the post-surgical clinical status is not always reported using common outcomes scales such as the modified Rankin Scale.

Therapeutic risk

- Systematic reviews of surgical outcomes are often hindered by center-specific biases, patient selection, and AVM subtype selection (e.g., location, size, etc.) [57, 58]. Those reporting large literature reviews showed a post-operative mortality of 3.3 % and permanent morbidity between 1.5 and 18.7 % [59]. A more recent meta-analysis reported a case fatality rate of 1.1 per 100 person-years following microsurgery in 2549 patients. Complications leading to permanent neurological

deficits or death were found in a median of 7.4 % (range 0 to 40 %) [38••]. Large (grade 4–5) AVMs carry a higher surgical risk. Complete removal of these malformations leads to mortality and morbidity rates of about 20 % even in experienced centers [60]. Most reports do not segregate therapeutic risks between ruptured and unruptured AVMs. Those unbled with normal neurologic status have a risk of clinical worsening after surgery more than twice as high as the risk for those with prior hemorrhage [53]. Differences in outcome reporting between studies with or without independent neurological follow-up have also been noted. Reported permanent deficits range from 11 % in the former to 37 % in the latter analyses [61, 62].

Endovascular embolization

Indications and methods

- Endovascular embolization was originally developed as an adjuvant method to facilitate subsequent microsurgery or radiotherapy [63–65]. Superselective catheterization and occlusion of arterial feeders while sparing the draining vein is utilized to reduce AVM nidus size or high-flow shunts, target specific angioarchitectural features, or achieve palliative flow reduction [66]. Less or no longer used substances include barium-embedded silastic pellets, thrombogenic metal shapes, silk sutures, ethyl alcohol, and polyvinyl alcohol particles. Still in use are balloons, metal coils, and especially liquid embolic agents. The most used of the latter are *N*-butyl cyanoacrylate (NBCA) and ethylene vinyl alcohol [67•, 68]. Glue delivery is aimed to occlude arteries feeding the AVM but sparing those feeding healthy brain tissue. Depending on center-specific treatment algorithms, embolization is used as adjunctive therapy only or with the goal of complete occlusion of those AVMs deemed curable [69–71]. Embolization is also used to reduce venous congestion or high-flow shunting as partial treatment to reduce headaches, seizure frequency, and neurological deficits.

Classification

- In contrast to AVM surgery, the widespread use of a particular AVM classification scheme is lacking for embolization. To describe the status of an AVM, the Spetzler-Martin grading system is often used, although relevant anatomical and functional features differ from AVM surgery: Size still plays an important role for the assessment of curability [66, 69]. However, number of feeding arteries, accessibility via microcatheter, location in eloquent regions, deep feeders, fistulous versus plexiform AVM types, shunt flow volume, and number and configuration of

draining veins all impact on the risk of endovascular treatment [66, 72, 73•, 74].

Therapeutic risk

- Advanced techniques are used to address specific vascular situations like transvenous embolization [75], balloon-assisted embolization [76], and double arterial catheterization [72] which have been used to reduce complications in special situations. These procedures need to be validated further. Treatment risks include occlusion of arteries supplying healthy brain tissue, perforation of arterial feeders, and occlusion of draining veins before obliteration of arterial blood flow to the fistula. Numerous self-reported complication rates range from 9 to 22 %, depending on treatment goals, techniques, and AVM selection [44]. Reports of independent neurologic assessment remain rare. In this setting, new neurologic deficits were reported in 13 % (3 % disabling) and mortality of less than 1 % [77]. The advent of the better controllable, less adhesive agent Onyx initially seemed to promise better outcome rates, but comparisons with NBCA showed that they were in the same range [67•, 78–80]. Meta-analyses report case fatality rates of 0.96 per 100 person-years and permanent morbidity and mortality rates of 6.6 % (median, range 0–28 %) with obliteration rates of 13 % (median, range 0–94 %) and recurrent hemorrhage rates after embolization of 1.7 per 100 person-years [38••]. Experience of the treating center seems to have an effect on therapeutic outcome [81•].

Stereotactic radiotherapy

Methods and indications

- Options for radiotherapy include gamma knife, linear accelerator, and proton beam [42]. Radiation therapy involves multiple, focused beams directed at the malformation nidus. The goal is to generate vascular injury of the endothelium with proliferation of smooth muscle cells in the vessel wall with subsequent thrombosis. Originally used to treat small AVMs (diameter <3 cm) in regions difficult to access by neurosurgery such as small deep malformations in the basal ganglia [82], the indications for radiotherapy have expanded to a large group of AVMs [83, 84]. Advances in radiation techniques regarding planning tools, improved hardware accuracy, and staged-volume, staged-dose, and hypo-fractionated irradiation techniques continue to evolve. Radiation therapy is used either as adjunct therapy or as single-

modality treatment of AVMs [85•, 86, 87•, 88]. The attractiveness to the patient is its non-invasive nature. The major disadvantage of radiotherapy is that the obliteration may take years to complete and that during the interval the hemorrhage risk remains [89].

Classification

- Although the use of the Spetzler-Martin grading system is applied to AVMs undergoing radiosurgery, some features more specific to AVM treatment outcome in radiation therapy have led to proposals of separate grading systems. One of them uses the main predictors of radiotherapy outcome namely AVM volume, patient age, and location of the lesion (frontal or temporal carrying the lowest risk; basal ganglia, thalamus, or brainstem the highest; other locations intermediate). Additionally, each feature receives a multiplier according to its attributable part of the total treatment risk [90].

Therapeutic risk

- The major pitfall in stereotactic radiosurgery is the risk of hemorrhage until obliteration is achieved [89, 91]. Some authors have even stated an increased annual risk of hemorrhage after irradiation [92], while others report a decrease of hemorrhage risk even before AVM occlusion occurs, but only in patients with previous AVM hemorrhages [93]. Other risks include (often reversible) edema, radiation necrosis of healthy brain tissue, cyst formation, cranial nerve lesions, and intracranial arterial stenosis [44, 94]. Multicenter analyses and literature reviews describe radiation-induced permanent neurologic deficits in 6 to 8 % [94, 95]. A current meta-analysis reports case fatality rates of 0.50 per 100 person-years and permanent morbidity and mortality rates of 5.1 % (median, range 0–21 %) with obliteration rates of 38 % (median, range 0–75 %) and recurrent hemorrhage rates after radiotherapy of 1.7 per 100 person-years [38••]. Large AVMs can be targeted with combined treatment approaches or techniques like staged-volume treatment [85•, 96], but radiotherapy of large malformations carries a higher treatment risk. A recent retrospective analysis describing outcomes of patients inferred would have been eligible for A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) reported an annual risk of stroke or death of 2 % for the first 5 years after irradiation, declining thereafter. Patients with small AVMs (<5.6 cm^3) had a much lower risk [97•].

Combined treatment

Rationale

- AVMs too large or inconveniently located to remove with surgery alone, with deep feeding arteries or high-flow shunts increasing the surgical risk, with diffuse niduses, and with associated or intranidal aneurysms inferred to worsen the risk of hemorrhage are often approached in staged treatments involving two or more treatment modalities [98]. Preoperative embolization, post-embolization radiosurgery, and post-radiation surgery are the most commonly used practices [61, 65, 99]. Although deemed helpful by some groups [64, 100], failures to improve outcome [101] or lower AVM obliteration rates have been described by others [102, 103]. Lacking uniform recommendations or treatment algorithms, decisions to treat AVMs in a combined approach are mostly based upon individual center experience, available expertise and technical equipment, and personal convictions [42]. They are not based on what is generally recognized as scientific evidence but on single- or multicenter observations and systematic literature reviews with varying treatment results and side effects.

Therapeutic risk

- It is yet unproven that combination treatment leads to a lower treatment-related complication rate than single-modality treatment. Usually, AVMs treated with multiple disciplines either are large or carry other features unfavorable for complete removal or obliteration, making direct comparisons with single-modality treatment results difficult. Some series report complication rates suggestive of multi-modality benefit [104], and others reveal increased side effects, combining those of all applied interventions [105]. Outcomes assessed by independent study neurologists are rare. In one such series of 119 patients treated with embolization and surgery, treatment-related complications were observed in 42 % (non-disabling) and 5 % (disabling) [61]. New deficits were observed significantly more often in patients with unbled AVMs (58 %) compared with those who had ruptured AVMs (27 %, p=0.001).

Medical management

Background and risk

- Once an AVM has bled, the incentive is strong to obliterate or remove the malformation if possible and with acceptable risk. The situation is different for patients with unbled AVMs for whom the natural course risk may be lower and treatment risks higher than in those who have hemorrhaged [3, 8, 42, 44].

Unfortunately, there is currently no medication available that will rid the patient of an AVM or even lower its risk of hemorrhage. Promising analyses have related expression of MMP-9 to AVM hemorrhage and shown its suppression by minocycline and doxycycline, but their use as vasculostatic drugs has not evolved beyond feasibility and pilot studies [106, 107]. However, medical management of AVMs is not simply a "do nothing" approach but involves careful evaluation of the natural course risk of each individual AVM patient. Treatment recommendations unbiased towards any specific intervention by an interdisciplinary team, also taking into account the patients' wishes, anxieties, and life plans, are an important step to help with the decision for or against interventional management. It is also helpful to cite the low morbidity usually associated with hemorrhage, which can be described as "bleeding" or "leak" instead of the frightening term "rupture," which suggests the violence of that from an aneurysm. Advising the patient on activities of daily life and pharmacological treatment of neurologic symptoms like seizures or headaches are important steps to maintain a good quality of life. Clinical and, if warranted, brain MRI follow-up may help to detect changes in physical symptoms or morphological features that suggest reevaluation of the initial management decision.

Interventional versus medical management

- There is little doubt that AVMs presenting with hemorrhage or even uncontrollable seizures should be completely removed or obliterated if treatment can be performed with an acceptable risk. Treatment planning should involve the methods deemed best for the individual patient to achieve this goal.
- However, there is limited scientific evidence on what to do with an unbled AVM that has caused no or only medically treatable symptoms. To date, there is only one published randomized clinical trial addressing the issue [34••], with a recent publication-based study confirming its results [35••]. Because of the large amount of international recognition and discussion that have appeared before [108], during [109, 110], and after

Table 1. Event rates (death or symptomatic stroke) by Spetzler-Martin grades in the ARUBA trial (as treated)

Spetzler-Martin grade	Interventional treatment (*n*=98)		Medical management (*n*=125)		*p* value
	n patients	% events	*n* patients	% events	
I	28	14.3 %	37	5.4 %	0.22
II	37	43.3 %	34	2.9 %	<0.001
III	28	57.1 %	34	8.8 %	<0.001
IV	5	0 %	18	22.2 %	0.25

completion of the trial [111–117], a more detailed description seems warranted. The ARUBA trial (A Randomized Trial of Unruptured Brain Arteriovenous Malformations) was organized in 2006 to compare the risk of death and symptomatic stroke in patients with an unruptured brain AVM allocated to either medical management alone or medical management with interventional therapy [34••]. Patients were included when the interdisciplinary team of neurologist, neurosurgeon, endovascular neuroradiologist, and radiation therapist concluded that (1) there is clinical equipoise on the decision to treat, i.e., no clinical or anatomical-morphological situation favoring treatment or conservative approach in the experts' opinions, (2) the AVM was deemed completely treatable with acceptable risk, and (3) the patient agreed to the randomization process. Regular follow-up with clinical investigations by a study neurologist and imaging studies at predefined intervals were conducted. Lacking published and internationally accepted treatment algorithms, the choice of best possible interventional treatment was left to the decision of each treating center. The trial was funded by the National Institute of Neurological Diseases and Stroke (NINDS), the institute among those at the National Institutes of Health (NIH) dealing with stroke. In such trials, the first funding cycle is typically limited to 5 years. A distinguished independent data and safety monitoring board (DSMB) appointed by the NINDS met at predefined intervals. The goal was to include 400 patients in the trial. In April 2013, with 226 subjects randomized, the DSMB recommended halting the randomization phase after a planned interim analysis had demonstrated superiority for the medical arm [118••]. A more than fivefold increased risk of death or symptomatic stroke was found for those undergoing interventional treatment (HR 5.26, 95 % CI 2.63–11.11, Fig. 1) [116]. The risk of major neurologic deficits was also increased (RR 2.77, 95 % CI 1.20–6.25, Table 1) [34••]. Further follow-up was strongly recommended to determine whether the disparity would persist, with AVMs being lifelong diseases and the risk of treatment-related side effects being highest around the time of treatment. However, the priority for further funding was judged by a Study Section and NINDS Council to be too low for funding based on the assumption that the disparity between the two treatment arms was unlikely to change in the requested additional 5-year follow-up period. ARUBA was the first randomized clinical trial addressing the need for invasive treatment in unruptured AVM. It was conducted following the highest scientific standards by experienced centers and produced widely accepted results. Criticisms of the trial focused on small sample size, limited follow-up, alleged substandard interventions, randomization bias by large centers based upon ethical equipoise, and suggestions the observed deficits were transient and minor

[113–115]. Most of the criticisms have been rebutted in the original publication. Some generated further analyses and research projects that are currently in preparation [118••].

Compliance with Ethics Guidelines

Conflict of Interest
A. Hartmann and J.P. Mohr declare no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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