

AHA/ASA Scientific Statement

Management of Brain Arteriovenous Malformations

A Scientific Statement for Healthcare Professionals
from the American Heart Association/American Stroke
Association

*The American Academy of Neurology affirms the value of this statement as an
educational tool for neurologists. (PENDING)*

*Endorsed by the American Association of Neurological Surgeons and Congress of
Neurological Surgeons (PENDING)*

Endorsed by the Society of NeuroInterventional Surgery (PENDING)

Authors



Colin P. Derdeyn, MD, FAHA, Chair; Gregory J. Zipfel, MD, FAHA, Vice-Chair; Felipe C. Albuquerque, MD; Daniel L. Cooke, MD; Edward Feldmann, MD, FAHA; Jason P. Sheehan, MD, PhD; James C. Torner, PhD, MS, FAHA;

On behalf of the American Heart Association Stroke Council



Slides Prepared by Members of the Stroke Professional Committee



- Daniel L. Cooke MD
- Majaz Moonis MD, MRCPI, FRCPE, FAAN, FAHA, FAASM

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Introduction



- Brain Arteriovenous Malformations (bAVMs) are uncommon and may present with intracranial hemorrhage (ICH).
- Treatment options include conservative management, surgical resection, stereotactic radiosurgery, endovascular embolization, or combinations of these treatments.
- The primary goal of these interventions is to prevent hemorrhagic stroke.
- The purpose of this statement is to review the current data, make recommendations for management of patients with bAVMs, and to provide an update to the 2001 AHA statement.



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Methods

- Online searches were conducted independently by each author of all English-language papers on bAVMs in humans, following the AHA Task Force on Practice Guidelines for literature searches (https://professional.heart.org/professional/GuidelinesStatements/PublicationDevelopment/UCM_320470_Methodologies-and-Policies-from-the-ACCAHA-Task-Force-on-Practice-Guidelines.jsp).
- The chair and vice chair revised the document in response to peer review, and the document was again sent to the entire writing group for additional suggestions and approval
- Formal recommendations with grades and levels of evidence include the Primary and Secondary Prevention Guidelines and the Intracerebral Hemorrhage Guideline. This Scientific statements is more narrowly focused serves to increase the knowledge and awareness of healthcare professionals.

Epidemiology and Biology

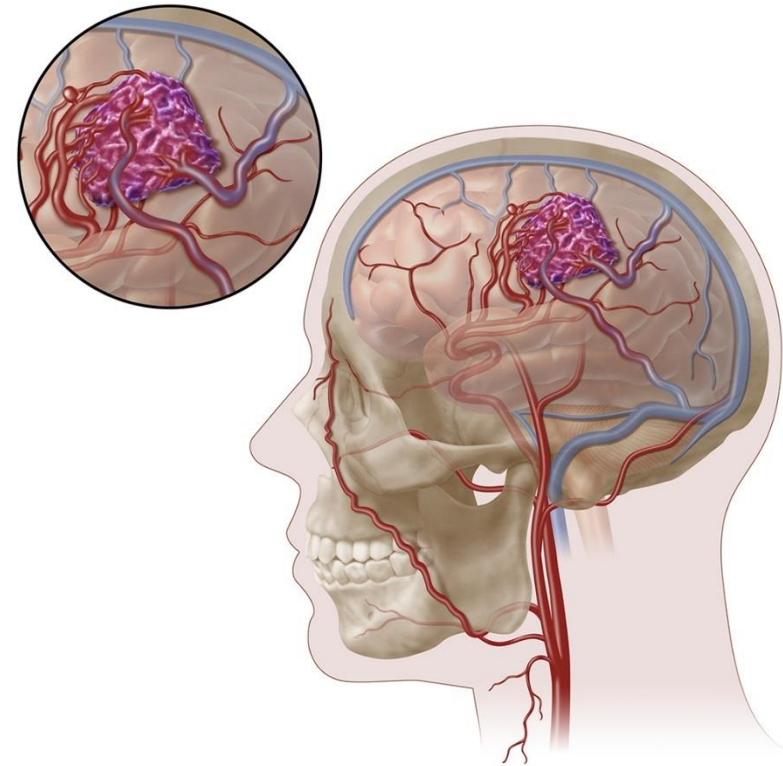


- Brain AVMs have an asymptomatic prevalence on brain Magnetic Resonance (MR) studies of 0.05% (95% CI 0.01-0.10), and asymptomatic or symptomatic detection of bAVM in the population of 10–18 per 100,000 adults (0.010-0.018%).
- New detection rate (incidence) is approximately 1.3 per 100,000 person-years.
- Symptomatic bAVMs manifest with hemorrhagic stroke (58%), epileptic seizure(s) (34%), or other symptoms such as progressive neurological deficit (8%).

Epidemiology and Biology



- Brain AVMs are characterized by direct connections from artery to vein with an intervening tangle of abnormal dilated channels, neither arterial nor venous, termed the nidus.
- Blood is shunted from artery to vein through the nidus, resulting in higher than normal flow in both feeding arteries and draining veins, and higher than normal pressure on the venous side.



Epidemiology and Biology



- Factors that may contribute to complex vascular physiology include high flow rates and shear stress, nidal flow impedance, and/or venous outflow obstruction.
- Anatomic features associated with hemorrhagic presentation include the presence of intranidal aneurysms (large arrow) or deep venous drainage (drainage into the galenic system), and deep or infratentorial location.



Epidemiology and Biology



- While new molecular genetic information has no immediate impact on current recommendations for management bAVM, it has great potential for defining future therapeutic options or rupture risk.
- Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant vascular disease and the most common genetic cause of bAVMs with the causative mutations for HHT involve haploinsufficiency of signaling genes for transforming growth factor (TGF)- β .
- Mutations in RASA1 are associated with the capillary malformation-AVM (CM-AVM) syndrome.
- Evidence supporting multi-hit somatic mutation in AVM pathogenesis along with de novo bAVM observation support the idea that many of these lesions are acquired and not congenital.

Natural History



- The natural history of bAVMs often centers on stroke with many studies focusing on ICH event rate, as it represents the most common and morbid clinical manifestation of the disease.
- The untreated clinical course of bAVMs is based on observational research studies of everyday clinical practice and the conservative management group in the ARUBA trial.
- ICH is not the only long-term consequence of bAVMs and many patients may develop seizure disorders.

Natural History



- An individual patient data meta-analysis of 2,525 patients with 141 ICHs during 6,074 person-years of follow-up in a variety of population- and hospital-based studies provides the most reliable data on bAVM untreated clinical course.
- The annual risk of ICH is 2.3% (95% CI 2.0 to 2.7) per year over 10 years, however the annual risk differs according to whether a bAVM was unruptured (1.3% [95% CI 1.0 to 1.7]) or ruptured (4.8% [95% CI 3.9 to 5.9]) when first diagnosed.

Natural History



Annual Rupture risks for ruptured and unruptured bAVM

Study	Number of patients	Year	Study type	Annual ICH risk (unruptured)	Annual ICH risk (ruptured)
Kim	2,525	2014	Pool patient level data	1.3 (1.0 – 1.7)	4.8 (3.9 – 5.9)
Gross	3,923	2013	Meta-analysis	2.2 (1.17 – 2.7)	4.5 (3.7 – 5.5)
Abecassis		2014	Review article	2.1 to 4.1	
Mohr	233	2016	Prospective clinical trial	2.0 (0.9 – 4.5)	

Natural History



- The most consistently reported prognostic factor for ICH after diagnosis is initial presentation with ICH.
- Increasing age is another prognostic factor significantly associated with future ICH with a 1.34-fold increase per decade.
- Exclusively deep venous drainage may be another prognostic factor for ICH, conferring a 1.6-2.4-fold increase in annual risk.
- Deep AVM nidus location and associated arterial aneurysms may also be prognostic factors, though better-powered studies are needed.

Natural History



Hazard Ratios for rupture risk for clinical and anatomic features from longitudinal studies of unruptured bAVMs

Study	Number	Year	Study Type	Exclusively Deep Venous Drainage	Any Deep Venous Drainage	Increasing Age at Diagnosis	Deep Nidus Location	Associated Aneurysms	Female Gender	Size < 3 cm
Kim	2,525	2014	Pooled patient level data	1.60 (0.95 – 2.68)		1.34 (1.17 – 1.53)			1.49 (0.96-2.30)	1.02 (0.90-1.16)
Gross	3,923	2013	Meta-analysis	2.4 (1.1 – 3.8)	1.3 (0.9 – 1.75)	1.0 (0.4 - 1.6)	2.4 (1.4-3.4)	1.8 (1.6-2.0)	1.4 (0.6-2.1)	1.0 (0.8 – 1.2)

Natural History



- Angioarchitectural risk factors for ICH from smaller series include deep and infratentorial location (OR 2.718, $p = 0.007$), single draining vein (OR 0.404, $p = 0.008$), venous varices (OR 0.488, $p = 0.018$), and aneurysm all type (OR 8.541, $p = 0.002$) or flow-related (OR 2.923, $p = 0.002$).
- bAVM size has been implicated as a risk factor, though in the larger cohorts this association has not been replicated.
- There is no evidence that any of HHT or RASA1 genotypes confer higher ICH risk or a particular bAVM appearance.

Natural History



Angioarchitectural features associated with ruptured bAVMs (retrospective studies comparing ruptured to unruptured bAVMs (potential prognostic significance)

Study	number	Year	Larger Size	Aneurysm	Venous stenosis	Venous ectasia	Exclusively deep draining	Single draining vein
Stapf	464	2006	Yes	Yes			Yes	Yes
Sahlein	122	2014		Yes	Yes			Yes
Alexander	519	2015				Yes	Yes	Yes
Lv	302	2011		Yes		Yes	Yes	Yes

Natural History



- Clinical outcomes from bAVM ICH is less well-defined in part due to entanglement with treatment effects.
- Admission GCS, age, and ICH volume are similarly predict bAVM-related ICH clinical outcomes as in the setting of primary ICH.
- There is limited data describing angioarchitectural details and ICH-related clinical outcomes, though AVM volume does not appear associated ICH volume.
- There is evidence that posterior fossa bAVMs may present more often with smaller ICH volumes and flow-related aneurysms as well as poorer clinical outcomes relative supratentorial bAVMs.

Natural History



- ICH presentation is more common in children (56% vs. 43%) , though similar annual ICH rates compared to adults (2.0% vs. 2.2%).
- There is no evidence in support of an increased rate of ICH during pregnancy or puerperium.

Natural History



- Brain AVMs may cause focal or secondary generalized seizures, or both
- The 5-year risk of first seizure is 8% (95% CI 0-20%) for patients with bAVM and in the setting of ICH or focal neurologic deficit increased the risk of seizure to 23% for patients with bAVM.
- The 5-year risk of developing epilepsy following a first seizure was 58%.
- Angioarchitectural features associated with seizures include a cortical location, superficial venous drainage, varices, and positioning within the frontal and particularly the temporal lobe.

Imaging Diagnosis and Evaluation



- The imaging evaluation of bAVMs may be separated into three clinical settings: diagnosis, treatment planning, and follow-up.
- The definitive diagnosis of a bAVM is currently by digital subtraction angiography (DSA), although many bAVMs can be reliably identified by CT (computed tomography) and MR (magnetic resonance) imaging, including angiographic imaging (CTA and MRA).
- Non-contrast CT has > 90% sensitivity for acute subarachnoid hemorrhage and hemorrhagic stroke and though limited in detecting bAVMs, it can demonstrate features, including enlarged or calcified vessels along the margin of the hemorrhage or regions of increased density corresponding to the vascular nidus, suggestive of an underlying vascular anomaly.

Imaging Diagnosis and Evaluation



- For any new ICH with non-contrast CT findings and/or epidemiological and/or clinical variables suspicious for a secondary vascular etiology and cross-sectional angiogram should be performed.
- CTA and MRA have excellent accuracy for the detection of secondary vascular anomalies in the setting of ICH.
- Both CT and MR provide information about the bAVM and the adjacent brain, this latter information essential as it relates to assessing treatment planning.

Imaging Diagnosis and Evaluation



- For a subset of acute hemorrhagic bAVM patients as well as those without ICH presentation, MR may identify prior subclinical microhemorrhage (white arrow) using susceptibility-weighted imaging.
- MR offers the ability to perform advanced methods including temporal encoding, functional imaging, and flow-related parameters all of which may help in treatment planning.



Imaging Diagnosis and Evaluation



- Digital subtraction angiography (DSA) is the reference standard for the diagnosis providing the most detailed and accurate information on bAVM angio-architecture and hemodynamics.
- In addition to bAVM size, location, and venous drainage pattern other angioarchtetural details that should be noted include: number of veins, presence of subependymal venous involvement, number of veins reaching a sinus, venous ectasia, venous reflux or occlusion, flow-related or nidal arterial aneurysms, angiopathy, angiogenesis, nidal border, and/or pial-pial collaterals.
- Associated aneurysms occur 15-30% of patients, and may be remote, arising from arterial afferents, or intra-nidal in location, with the latter being associated with a higher annual rate of ICH.

Imaging Diagnosis and Evaluation



- There is limited data on the utility of imaging surveillance for untreated bAVMs, though long term monitoring is important after treatment, particularly following stereotactic radiosurgery and in the pediatric setting.
- DSA remains the reference standard, though MRA has improved in its ability to assess for residual bAVM, particularly in the post radiosurgical treatment setting.

Treatment: Overview



- I. The definitive treatment of bAVMs should be complete elimination of the nidus and the arteriovenous shunt. Partial nidal obliteration does not appear to reduce hemorrhage risk
- II. Additional interventions to reduce hemorrhagic risks with partial bAVM obliteration
 - I. Microsurgical resection. This may be performed primarily or after endovascular embolization to reduce bleeding risks during surgery and facilitate complete and uncomplicated removal.
 - II. Stereotactic radiosurgery. Which may be done primarily or after embolization to reduce nidal volumes and potentially improve nidal obliteration rates.
 - III. Endovascular embolization .

Treatment: Microsurgical Resection



- I. Microsurgical resection via craniotomy is a common approach for treating patients with bAVMs with a goal to achieve definitive cure.
- II. The sequential steps in this approach include:
 - a. Craniotomy to obtain adequate exposure to the bAVM including its arterial feeders and venous outflow
 - b. Isolate and divide its arterial feeders;
 - c. Circumferentially dissect the nidus from the adjacent brain parenchyma and surrounding neurovascular structures
 - d. Disconnect the venous outflow
 - e. Wound closure.



Microsurgical Resection: Advantages and Disadvantages



Advantages

- High rate of complete nidus obliteration
- Ability to immediately eliminate hemorrhage risk
- Long-term durability.

Disadvantages

- Invasiveness,
- Prolonged length of recovery
- Procedural risks.

Adjuncts to Improve Outcomes with Microsurgery



- Functional magnetic resonance imaging (fMRI) and diffusion tensor imaging-based tractography (DTI) have been applied to more accurately determine the proximity of bAVMs to eloquent cortex and critical white matter tracts
- Stereotactic neuronavigation has been used to permit smaller, more accurate, and more effective approaches to bAVM surgery. This technique involves quantitative spatial fusion of the patient's pre-operatively obtained CT and/or MR images with a fiducial coordinate system that permits guidance of surgical exposure and real-time localization of the bAVM and surrounding neurovascular structures
- Intraoperative vascular Imaging using DSA, Fluorescein videoangiography to map angioarchitecture
- Adjunct endovascular embolization aims to:
 - Reduce in flow and/or nidus volume that would permit safer surgical removal
 - Treatment of feeding artery and intra-nidal aneurysms.



Spetzler-Martin (SM) Grading Scale for AVMs



Spetzler-Martin Grading Scale for AVMs	
CHARACTERISTIC	NUMBER OF POINTS ASSIGNED
Size of AVM	
Small (<3cm)	1 point
Medium (3-6cm)	2 points
Large (>6cm)	3 points
Location	
Non-eloquent site	0 points
Eloquent site*	1 point
Pattern of venous drainage	
Superficial only	0 points
Deep component	1 point
*Sensorimotor, language, visual cortex, hypothalamus, thalamus, internal capsule, brain stem, cerebellar peduncles, or cerebellar nuclei	

SM grade I = 4% (CI: 2-7%); SM grade II = 10% (CI: 7-13%); SM grade III = 18% (CI: 15-22%); SM grade IV = 31% (CI: 25-37%); and SM grade V = 37% (CI: 26-49%)¹⁵². These results demonstrate microsurgical removal is best suited for low-grade bAVMs (SM I and II), while surgical removal of high-grade bAVMs (SM IV and V) carries high risk of poor patient outcome.

Management: Unruptured bAVMs: Further Categorization



SM grade III bAVMs are subcategorized based on specific combinations of size, location, and venous drainage.

1. SM grade III- bAVMs (combination of small size, eloquent location, and deep venous drainage) have good surgical outcomes
2. SM grade III bAVMs (combination of medium size, non-eloquent location, and deep venous drainage) and SM grade III+ bAVMs (combination of medium size, eloquent location, and superficial venous drainage) have worse surgical outcomes similar to that reported for high-grade bAVMs

Management of Unruptured Aneurysms

Lawton-Young Supplementary Grading Scale



- Improving the predictive value of bAVM outcomes
Supplementing the traditional SM grading scheme:
 - 1) patient age (<20 y = 1 point; 20-40 y = 2 points; >40 y = 3 points)
 - 2) bleeding or hemorrhagic presentation (yes = 0 points; no = 1 point)
 - 3) Nidus configuration (compact = 0 points; diffuse = 1 point)
 - More accurate at predicting patient outcome vs. the SM system alone.
 - This scale has been referred to as the Lawton-Young supplementary grading scale and has been validated in a separate cohort of 1009 patients

Results of Microsurgery



Study	Number	Year	Design	% Ruptured	Spetzler Martin Grade	Surgical risk (95% CI)	Obliteration Rate
Davidson ¹⁴³	296	2010	Prospective Database	49% ruptured	1-2	0.7% (0-3%)	96.9% overall
	65				3-4 (noneloquent)	17% (10-28%)	
	168				3-5 (eloquent)	21% (15-28%)	
Spetzler ¹⁵² *	250	2011	Pooled Case Series	NR	1	4% (2-7)	NR
	485				2	10% (7-13)	
	455				3	18% (15-22)	
	218				4	31% (25-37)	
	68				5	37% (26-49)	

* Spetzler et al., reported pooled surgical outcomes from 7 studies of ruptured and unruptured bAVMs, including the original dataset for the outcome scale. Two studies were published after 2000, Davidson et al.¹⁴³ and Lawton et al.¹⁴⁹.

CI = confidence intervals; NR = not reported.



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Stereotactic Radiosurgery (SRS)



- SRS is used in patients where it is very risky to perform micro resection either due to the AVM itself or the patients medical condition.
- Leads to endothelial cell proliferation, necrosis, concentric vessel wall thickening and eventual closure.
- Time to obliteration is prolonged and complications of radiation injury, edema and cyst formation as well as early hemorrhage are some of the disadvantages of the procedure.
- Long term follow-up shows an obliteration rate of 70-80%
- In situations where SRS is the best option and resulted in incomplete obliteration, repeat SRS can be considered

Unruptured bAVM: Radiosurgery



Radiosurgery may be the best option

Series	Patients	Follow-up (months)	Radiation Induced changes	Annual hemorrhage rate	Clinical deterioration	Cause of deterioration	Obliteration Rates
Ding	444	86	13.7% (temp) 2% (permanent)	1.6%/yr	12.3%	Early hemorrhage	62%
Starke	2236						60.3%
Pollock	174	64	4%	11.5%at 10years	4%	Radiation necrosis	78.9%



Pre-treatment Radiation Scales

Factors and Validation



- Age, lesion size, location relative to eloquent cortex, number feeding vessels and draining veins
- In a study of obliteration outcomes in 139 patients undergoing radiosurgery, Taeshineetanakul et al. reported factors predictive of bAVM obliteration. These included the following
 - bAVM size (OR 0.88, CI 0.81 – 0.96),
 - non-eloquent location (OR 3.2, CI 1.29 – 7.93)
 - low flow pattern (OR 3.47, CI 1.6 – 7.53)
 - Absence of perinidal angiogenesis (OR 2.61, CI 1.21 – 5.64)

Endovascular Treatment



- Commonly used as an pre-procedural adjunct microsurgery or SRS with the aim of reducing vascularity and thus reducing the chances of other subsequent interventional complications
- Sometimes used as a stand alone procedure to obliterate AVMs. Here ethyl vinyl alcohol copolymer (EVOH) or NBCA are used. Detachable micro -catheter tips are helpful in reducing complications
- As a palliative treatment to improve symptoms caused by vascular steal secondary to the bAVM

Embolization Scales



- A five point scale that takes into account the following
- Arterial Feeders (<3, 3-6. >6)
- Location of the bAVM
- Size >3 cm
- Diameter depth >6 cm
- Deep venous drainage
- Proximity to eloquent cortex

Complications of Embolization



- The two most common complications of embolization are intracerebral hemorrhage and ischemic stroke
- The causes of ischemic stroke include thromboembolic complications of catheterization as well as non-target embolization
- Brain hemorrhage may occur from vessel wall injury or AVM rupture.
 - Microcatheter or wire perforation of arterial feeders may occur owing to access through small tortuous pial arteries.
 - The AVM nidus may rupture during embolization or in the hours to days following the procedure. This may be due to inadvertent closure of the draining vein prior complete nidal elimination or to other in the nidal pressure flow dynamic changes

Multimodal Treatment



- Initial single or staged embolization with the aim of reducing vascularity and bAVM volume
- Subsequent microsurgery or SRS
- Follow-up radiological and angiographic studies to determine the outcomes of the procedure

Studies of Multimodal Approach and outcomes: embolization with subsequent SRS

Study	Number	Year	Modalities	Obliteration rates	Hemorrhage prior to obliteration	Permanent Complication rates
Mathis ²¹⁸	24	1995	Embo/SRS	50%	0	Embo 0/SRS 4%
Gobin ²¹⁷	30	1996	Embo/SRS	60%	3.6%/year	Embo 12.6%/SRS 0
Mizoi ²¹⁹	29	1998	Embo/SRS	38%	1 patient	Embo 11%/SRS 0
Blackburn ¹⁹⁷	19	2011	Embo/SRS	84%	0	Embo 14%/SRS 5%

ARUBA Trial and Unruptured bAVMs



- Result of the single randomized trial ARUBA did not support interventional treatment as opposed to conservative management.
 - Primary Outcome: Stroke or Death
 - Interventional group 30.7%
 - Medical group 10.1%
 - Enrollment has been stopped and a longer follow-up of 5-years is ongoing.
- These results supported by a more recent prospective non-randomized observational study of 204 patients where medical management was superior to interventional treatment in reducing the likelihood of death, sustained disability or non-fatal symptomatic stroke
- Critique: bAVM time to rupture and bleed is long compared to the shorter follow-up in these studies which may confound results and exclusion of patients under 16 years of age.
 - ARUBA most interventional patients were treated with embolization alone or as an adjunct to surgery or SRS alone.
 - Results of surgery or SRS as primary treatments with low grade SM aneurysms may have yielded better outcomes.



Seizure control after various interventions for bAVMs

- After microsurgical resection of bAVMs, there is excellent seizure control with many series suggesting up to 90% (80% seizure free and 16% with medically controlled seizures in patients with preoperative seizures)
- Deep arterial perforator supply to the bAVM was associated with continued seizures
- With SRS 44-88% achieve complete or partial freedom from seizures. Complete obliteration of the bAVM was associated with the greater (88%) cure.
- Microsurgery is superior to radiosurgery and embolization in achieving seizure control (78%, 66% and 50%) respectively
- Results were replicated in a very large meta analysis

Headaches after bAVM treatment



- No clear incidence or prevalence reported
- This is an area that needs more attention
- It is empirically suggested to avoid vasoconstrictors that might increase the risk of rupture

Management of Ruptured bAVMs



- Management of ruptured bAVMs is similar to the management of unruptured bAVMs
- Use of surgery, embolization, SRS or a combination of these modalities
- Embolization may be used alone in very high risk cases or as a means of reducing the nidus facilitating subsequent surgery
- NBCA (N0butyl cyanoacrylate) and EVOH (embolization materials) are commonly used for embolization and detachable micro catheter tips improve the chances of complete obliteration through a catheter based intervention
- A continuum of care starting from prehospital notification to the emergency department with ready access to neurology, neuroradiology and neurosurgery are essential in management



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Supportive Care: Ruptured bAVMs



- In non-emergent cases transfer to NICU
- Anticonvulsants when patients have seizures
- Control of blood pressure, hyperthermia and cerebral edema as needed
- Refer to the ICH and AVM guidelines 2011 and 2015 from the AHA and ASA for complete management details.

Future options in the pipeline



Ongoing Research

- Presently the research base knowledge needs to be expanded to attempt to answer the following questions
 - Can case and bAVM selection determine whether conservative treatment or interventional treatment should be selected
 - Sub-selection in a new trial similar to ARUBA to see if low risk aneurysms are better treated conservatively or with intervention
 - Greater understanding of the molecular genetics for patient intervention

An ongoing registry capturing these various treatment options and devising a new trial such a ARUBA to specifically address management based on patient and bAVM selection is required.



Summary



- Uncertainties still exist regarding the best approach to management of bAVMs.
- While medical management of unruptured bAVMs seems to be superior to intervention, subsets of patients may do better in terms of reduced risk of rupture and seizures with intervention and complete resection.
- Microsurgery offers the best option in selected cases for prevention of cerebral hemorrhage and seizure control.
- Where microsurgery is not feasible, SRS and Embolization may be options.
- Long term follow-up of patients in the ARUBA trial and other prospectively collected data may provide more definite pathways to the best management of bAVMs.



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