

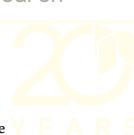


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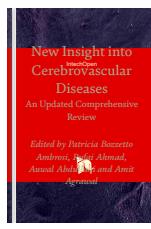
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FROM THE EDITED VOLUME

New Insight into Cerebrovascular Diseases - An Updated Comprehensive Review

Edited by Patricia Bozzetto Ambrosi, Rufai Ahmad, Auwal Abdullahi and Amit Agrawal

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Abstract

Topic: Chapter discussing the indications for treatment of brain aneurysms, endovascular techniques, tips and tricks.

1. Pathophysiology of aneurysms: Discuss the formation of aneurysms, current thinking of aneurysm development

2. Prevalence/Incidence of aneurysms: Discussion of current state of aneurysm prevalence and how it differs in different populations

3. Unruptured Aneurysms: Diagnosis, Management and Treatment: Imaging paradigms of brain aneurysms, current thoughts on how to follow aneurysms which are being observed, different treatment options for unruptured aneurysms, including clipping, coiling, stent assisted coiling, flow diverter stent, flow disruptors, including the medical management of stent placement

4. Ruptured Aneurysms: Diagnosis, Management and Treatment: Imaging paradigms of ruptured aneurysms, management options for comorbidities associated with aneurysm rupture, treatment options including coiling, clipping, flow diverter stents, flow disruptors

5. Complication Avoidance: Tips and tricks to avoid complications in the treatment of brain aneurysms.

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well as in chromosomal regions 1p34.3–p36.13, 19q13.3, Xp22 and 7q11. The strongest evidence for linkage was with a locus on 7q11 near the perlecan gene that encodes elastin, a protein that is involved in the preservation of vessel wall integrity.

1.2 Structural changes and hemodynamics

Cerebral arteries are prone to aneurysm formation due to presence of cerebrospinal fluid, sparse tunica adventitia, lower proportion of elastic fibers and disruption of internal lamina at bifurcation [,]. Blood is an active participant in the formation of aneurysms, its flow provides the mechanical triggers for reactions in the vessels at the level of the endothelium, while it is also a biological participant in the inflammatory cascade [,]. This dual function of blood contributes significantly to the degradation of the arterial wall in the formation of aneurysms [].

Cohort studies on people with a familial preponderance to saccular aneurysm have shown that the geometry of bifurcations around the circle of Willis adds additional stress to the vessel walls, given the significant shifts in flow velocity, dynamic forces, and shear stress. Thus, high flow across a wall that is not “designed” for the exposed pressures results in tissue injury and remodeling. The biological result may be plaque or may be an aneurysm, depending on the presence (or absence) of an intact media []. Fluid-dynamic models calculate and visualize wall shear stress or wall shear gradients, intra-aneurysmal flow, impingement zones, and flow patterns or velocities. Wall shear stress constitutes the degree of friction in the intracranial aneurysm wall that results from blood inflow and impingement into the aneurysm. High and low wall shear stress can both be present during aneurysm formation but the relevance of these flow conditions to the pathogenesis, growth and rupture of an aneurysm remain unclear []. The role of shear stress is very controversial, responsible for damage at specific phases of aneurysmal development and rupture. Some studies suggest the direct effect of shear stress on the vessel wall resulting in injury and degeneration of the wall’s media, leading to aneurysm formation. Others suggest that low shear stress in the aneurysm and the vessel wall may result in small thrombus formation, endothelial reactivity, and inflammation at the site, thus weakening the vessel.

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2. Prevalence and incidence of aneurysms

Although Unruptured Intracranial Aneurysms (UIA) are common [,]. Their prevalence is subject to changes due to the improvements in invasive and non-invasive imaging techniques, the increasing knowledge about the related factors that determines screening in asymptomatic populations and the increase in the life expectancy. Historically, the methods used to address prevalence were retrospective or prospective autopsy studies in the decades from 1950's to the earliest 2000's [] but non-invasive imaging studies have demonstrated higher prevalence and prevalence ratios compared to autopsy studies (PR 3·5, 95% CI 2·1–6·1). To study UIA, the Magnetic Resonance Angiography (MRA) is the most common method for detection in asymptomatic patients [] and compared to Intra-Arterial

Digital Subtraction Angiography (IA-DSA), systematic reviews have found no significant differences in the prevalence reported between these two imaging techniques (more details will be elucidated in the next section of this chapter). However, it's important to highlight that prevalence reported in non-invasive imaging studies can present limitations due to the interobserver agreement, training, experience, quality of equipment and expert's judgment [].

The IA characteristics are also a major concern in prevalence studies; technical limitations in regard to location, size and morphology can decrease the sensitivity and specificity of the diagnostic methods. Both, large and relatively small [] cohort's studies had shown that saccular morphology is the most common form of presentation and that among patients without history of subarachnoid hemorrhage (SAH) the distribution of IA in the internal carotid artery (ICA) and middle cerebral artery (MCA) are 24.8 and 22.7% [] respectively, however in patients with previous history of SAH, the prevalence is higher in the MCA. In regard to the size, modern imaging techniques can easily detect aneurysms from 2 mm, which is extremely important to determine the risks of possible treatments or natural history, so

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treat a patient based on their personal risk factors. Most of the large cohort's publications and meta-analysis have been done in populations where ethnicity diversity was limited, the impact of social stratus had not been assessed and criteria for collecting data and analysis was not standardized. Therefore, perfect epidemiological studies do not exist so, great efforts will be necessary to determine inclusion and exclusion criteria in future prospective cohorts.

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3. Unruptured intracranial aneurysms

Diagnosis of unruptured intracranial aneurysms (UIA) in most of the cases is incidentally during evaluations of other conditions [] because the vast majority are asymptomatic or have subtle manifestations. Only, 10 to 15.5% of patients have symptoms related to UIA []. These symptoms generally are associated to mass effect due to the aneurysm size and growth, rarely cranial neuropathy or even more rare with sentinel hemorrhage, due to minimal blood leaking with the consequent meningeal irritation []. Symptomatic UIA often present with neurological deficits as visual dysfunction, ocular nerve palsy, bilateral temporal hemianopsia and other neurological symptoms as headaches, embolic cerebral ischemia, poorly defined spells, and seizures [,]. Patients with symptomatic UIA need more attention because this can be a manifestation about riskier distribution and morphological [] characteristics of the aneurysm, and a warning sign of an impending rupture []. The diagnoses modality after incidental discovery of an UIA, is based on which imaging modality is more sensitive depending on aneurysms characteristics, patients related factors, medical history and moreover, methods available in each center. Therefore, there is no specific diagnoses algorithm for UIA. The decision of screening or further imaging after finding an incidental aneurysm is still on the specialist judgment. These considerations are discussed below:

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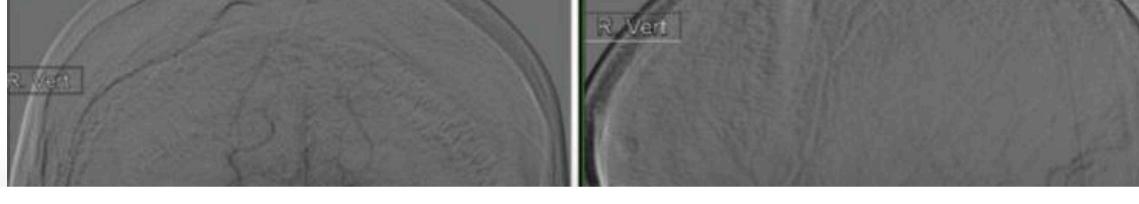
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treated aneurysms. MRA is not sensitive for patients with previously treated clipped aneurysms. For these patients CTA is preferred. MRA is still sensitive for previously coiled aneurysms. For patients treated with flow diverter stents either MRA with contrast or CTA can be used. If the patient had coils with any kind of stent, then MRA with contrast is the preferred modality.

Taken together the results of imaging for UIA, the neuro-interventional team consider the possible treatments for each patient based on the risks and benefits between prevent treatment and natural history, however due to lack of evidence of the natural history in some categories of UIA is not uncommon to balance the pros and cons between prevent treatment and aSAH outcomes. Some of the current available treatments will be discussed below.

3.1 Conservative management

First of all, having an aneurysm does not imply always the need to undergo surgical or endovascular treatment. Most of the UIA will never cause symptoms neither rupture or at least the probability of this events will not be over 1% per year. Therefore, many patients decide to take the risk of conservative management over the risks of preventive treatments. However, conservative management is not equal to doing nothing, this management bear intervention from the physician to educate well the patient about the risk factors that will increase the probabilities of rupture and an active participation of the patients to modify their risky habits. There is strong evidence that supports the conservative management when lifetime risk of morbidity and mortality is low [] as represented in .



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this frequency of time-interval is truly necessary. However, is not uncommon to have mixed factors in UIA patients, to make it clear, a systematic review showed that if hypertension and history of SAH are present (considering this both as major risk factors) in a patient under 70 years, with an <10 mm UIA in the anterior circulation, we will still be talking about a probability of risk of ~1% per year []. So, a standardized timing for imaging follow-ups according to each patients and aneurysm related factors does not exist, in part because aneurysm growing is discontinuous but the ELAPSS score (mentioned in) can be helpful to determine the need of follow-up at 3 or 5 years based on the risk of aneurysm growth []. These patients who choose conservative management live with a small very definite risk of rupture. Recently, a study showed that patients with untreated UIA, may decrease their quality of life (QoL) and moreover, trigger mental disorder as anxiety and depression [,] possibly due to the uncertainty of whether their aneurysm is going to burst and when.

3.2 Surgical management

Successful surgery is achieved in most of the cases by excluding aneurysms from circulation but currently, there is a lack of prospective, multicenter and randomized trials that report outcomes in a uniform way. Moreover, most of the studies were done in patients with previous aSAH like the ISAT trial [], which makes difficult to extrapolate those results to patients with UIA and no history of aSAH. The ISUIA-2 study did evaluate the surgical outcomes of nearly 1500 patients. They reported a mortality rate of 2.7% at 1 year and poor outcome (mRS 3–5) of 1.4% at 1 year. In this study, age > 70, posterior circulation and giant aneurysms were all associated with higher surgical morbidity and mortality. A meta-analysis done in the US with patients without previous history of aSAH that underwent to elective surgical clipping (SC) 14,411 and to endovascular treatment (EVT) 16,659 reported that iatrogenic stroke, intracranial hemorrhage, pulmonary complications, sepsis and status epilepticus were significantly higher after SC []. Moreover, the reduced recovery time and shorter stays in hospital [] play a major role in the final decision of patient to avoid surgery. Nowadays, SC is usually reserved to younger patients that will benefit more from an immediate occlusion of the aneurysm, less need to have follow-up imaging, less probability of retreatment and the ones with large and giant aneurysms or locations in the MCA.

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selection, recovery and risks. However, when leaving a stent placed in the artery it is important to manage the tolerance and adherence of the patient to dual anti-platelet therapy (DAPT) ([64]).



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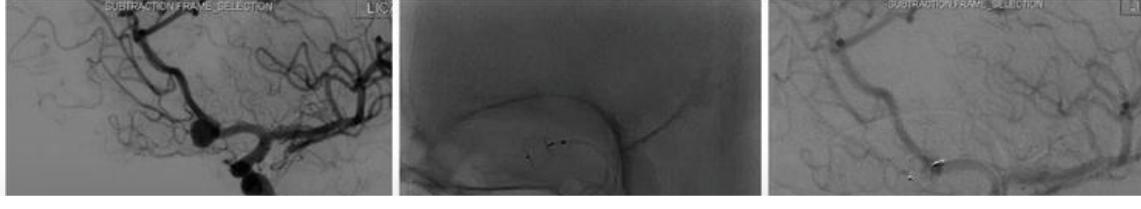
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placement [1], in this report overall complications were 3.4% and in multivariate analysis older age > 70, larger diameter > 15 mm and fusiform were identified as independent variables with higher rates of incomplete occlusion in 6-month follow-up. However, currently there is not a standardized scale to report radiographic outcomes that can be useful to meta-analysis studies or to new prospective randomized cohorts. Flow diverter stents are currently also limited usually to unruptured aneurysms, given the need for DAPT, however their use has found a niche in the treatment of ruptured blister aneurysms. Consequently, the next generation of this technology is looking into the possibility of special coating to mitigate the need for DAPT. Further investigation is still needed before this advancement will come to market.

3.7 Flow disruptors and web endoluminal bridge (WEB)

Although flow diversion devices can work out for many types of aneurysms as off-label uses; aneurysms located in bifurcations with wide neck and dome-to-neck ratio > 1 and < 2 remains a

challenge for this technology. Therefore, the WEB device was created in regard of these concerns in flow diversion and has proven promising to overcome those limitations. The WEB device is placed intra-aneurysm with a subsequent change in the blood flow at the aneurysm neck [1]. In European multicenter prospective studies, the WEB device placed in basilar, MCA, Acomm and ICA bifurcation showed 2.7% of morbidity and at 1 year of follow-up, 56% of aneurysm complete occlusion [2]. Owing this method does not require to put the patient under DAPT unlike the PED, it can be used also in aSAH cases. Further investigation is needed as to the long-term outcomes for this device (3 and 4).



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All the patients that can be good candidates for PED placement based on their UIA characteristics needs also to be eligible for prolonged DAPT. Acetylsalicylic acid (ASA) plus clopidogrel is the DAPT of reference used for preventing thrombosis in such procedures [5]. The laboratory tests pre and post-procedure are yet to be standardized; due to the risk of clopidogrel resistant (28–68%) [6], is has been considered necessary to assess platelet reactivity. High platelet reactivity (HPR) is related with thromboembolic events after stenting arteries [7]. Depending on institutional protocols, some neuro-interventional teams use the VerifyNow P2Y₁₂ assay which has been widely studied however, the results of this test may not be completely reliable [8] due to the fact that P2Y₁₂ response units (PRU) cannot differentiate aspirin-induced platelet inhibition in patients administered clopidogrel. Other studies recommend the use of the Thromboelastography (TEG), which is dynamic and real time tool to measure clot formation. The advantages of VerifyNow assay is that can be done very fast with instant results, however in patients with programmed procedures for UIA stenting this concerning may not be transcendental.

VerifyNow can overestimate the rate of clopidogrel resistance when compared to TEG. However, there is currently no randomized trials that have assessed the utility of this tests. Moreover, there's no strong evidence to support that the assessment of platelet reactivity improves clinical and imaging outcomes after stent placement. Nevertheless, the neuro-interventional teams at these days usually starts the DAPT with 325 mg of ASA and 75 mg of clopidogrel 7 days prior and maintain for 3–6 months after PED placement.

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4. Ruptured intracranial aneurysms

A 50-year-old female was preparing her children for school when she experienced a headache severe

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Signs of intracranial hypertension-nausea, vomiting, diminished level of consciousness

Epileptic seizures

Focal neurological deficits

Intraocular hemorrhage [,]

Terson syndrome: hemorrhage in vitreous humor, associated with high mortality []

Subhyaloid (pre-retinal) hemorrhage [].

4.2 Scoring system

Several scoring systems have been developed to predict patient outcomes for those with aneurysm related sub-arachnoid hemorrhage (a-SAH). The Hunt and Hess score and World Federation of Neurological Surgeons grading system are both used to predict patient outcome, and the Fisher grade helps to predict vasospasm [,].

The severity of neurologic impairment and the amount of subarachnoid bleeding on admission are the strongest predictors of neurologic complications and outcome []. Therefore, it is essential that patients with SAH be scored promptly after arrival and stabilization. The World Federation of Neurological Surgeons Scale (WFNSS) and the modified Fisher Scale are the most reliable and simple to perform [,]. Higher WFNSS and modified Fisher Scale scores are associated with worse clinical outcome and a higher proportion of neurologic complications. The modified Fisher scale is designed to predict the development of delayed cerebral ischemia (DCI) which is the most common cause of

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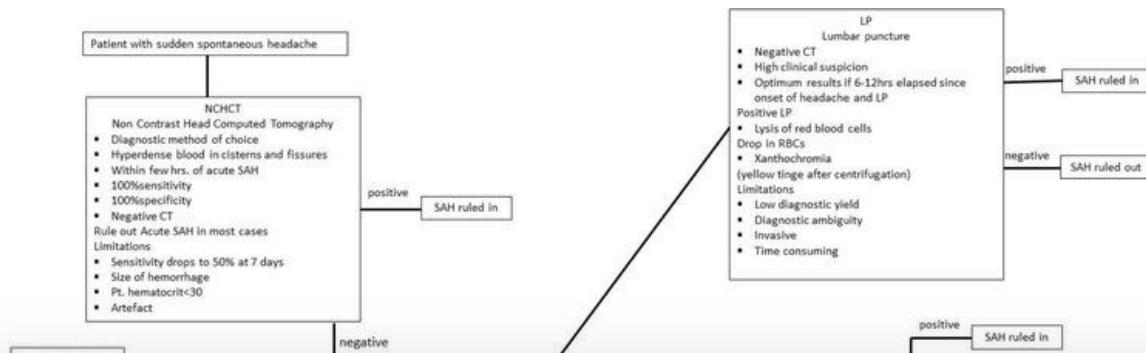
Grade	Appearance of blood on CT	Risk of cerebral hemorrhage
0	No sub arachnoid hemorrhage (SAH) or ventricular hemorrhage (VH)	0%
1	Minimal SAH, No VH in 2 lateral ventricles	6%
2	Minimal SAH, VH in 2 lateral ventricles	14%
3	Large SAH, No VH in 2 lateral ventricles	12%
4	Large SAH, VH in 2 lateral ventricles	28%

Table 3.

Modified fisher grading system [].

4.3 Initial imaging

With such a large number of patients presenting to the ED with a chief complaint of headache [, , ,], the description of headache can help differentiating those with a benign cause from those with an emergent etiology such as SAH. The diagnosis of SAH should be considered in any patient with a severe and sudden onset or rapidly escalating headache ().



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and effectiveness of antiepileptic drugs in SAH [].

4.6 Nimodipine

Delayed cerebral ischemia (DCI) is one of the most serious complications associated with SAH, occurring in one-third of patients surviving the initial hemorrhage and results in poor outcome in half of the patients with this complication []. Nimodipine is a calcium antagonist that is thought to reduce the rate of cerebral vasospasm by reducing the influx of calcium into the vascular smooth muscle cells. The administration of nimodipine to reduce the risk of poor outcome and DCI is the only level IA evidence recommended by the ASA [].

4.7 Blood pressure management

There is general consensus that hypertension should be controlled after SAH and until the ruptured aneurysm is secured. However, specific parameters for blood pressure have not been defined and data are sparse. Early retrospective studies suggest a higher rate of rebleeding with SBP greater than 160 mm Hg and severity of initial hemorrhage [1]. Therefore, the ASA and Neurocritical Care Society recommend maintaining SBP less than 160 mm Hg and mean arterial pressure less than 110 mm Hg before the ruptured aneurysm is secured to reduce the risk of rebleeding [2 , 3 , 4]. The ideal antihypertensive to use in SAH would be a parenteral agent that produces a rapid and reproducible dose response while concurrently minimizing adverse cerebral effects. Labetalol, nicardipine, and clevudine are agents recommended by the ASA [5].

4.8 Antifibrinolytics

When early definitive treatment of the ruptured aneurysm is not possible, antifibrinolytic therapies such as amino epsilon caproic acid or tranexamic acid can be considered to reduce the risk of early aneurysmal rebleeding. Early studies showed a reduction in rebleeding but an increase in cerebral ischemia with prolonged use of antifibrinolitics [6]. Neither aminocaproic acid or tranexamic acid is

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aneurysms considered suitable for either treatment. The results show that endovascular intervention with detachable platinum coils in patients with ruptured intracranial aneurysms can improve the chances of independent survival compared with neurosurgical intervention to clip the neck of the aneurysm.

4.12 Pipeline embolization device

The PED has mostly been used to treat unruptured aneurysms, whereas its use for acutely ruptured aneurysms has been limited and is theoretically contraindicated, given the need for dual antiplatelet therapy as it increases the risk of re-hemorrhage [7].

However, in certain cases of complex ruptured aneurysms, the PED may still serve as a good alternative (and sometimes may be the only available option) because these aneurysms are

anatomically and technically more difficult to treat using standard techniques []. Furthermore, certain anticoagulation protocols can be put into place to prevent the feared consequences associated with PED placement in ruptured aneurysms due to dual antiplatelet therapy. The standard management for the prevention of thromboembolic events when using flow diverters is pretreatment with aspirin and clopidogrel for 7–10 days prior to the procedure. When treating ruptured aneurysms with the PED in conjunction with this dual antiplatelet therapy, there is a concern for hemorrhagic complications. Chalouhi and colleagues [] described a new regimen for anticoagulation that was recently implemented in the hope of minimizing the risk of thromboembolic and hemorrhagic complications. In summary, the PED may be particularly helpful in acutely ruptured aneurysms that are not amenable to coiling or clipping. It can also be used in a staged fashion 1 or 2 weeks after partial coiling of the aneurysm dome. It is generally preferable to place an external ventricular drain if treatment with the PED is contemplated [].

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5.3 Endosaccular coiling

Coiling has likely reached its technological pinnacle. There has been little advancement in this technology over the last 5 years. One area of interest is in endosaccular flow disruptor type coils such as the Medina system. This is not as of yet FDA approved and remains to be seen whether this is efficacious or safe. Also the adjunctive tools for coiling continue to improve such as the Atlas stent, Pulserider stent and barrel stent which all are improvements for the treatment of bifurcation aneurysms and make difficult to coil aneurysms easier. We expect further improvements in these designs, and with improvements in deliverability. In addition to stents, the balloons available for balloon assisted coiling continue to improve in shape, design and deliverability which are particularly helpful in the setting of a ruptured small or wide necked aneurysm [].

5.4 Imaging and aneurysm rupture prediction

Currently other than aneurysm size, and certain bio-social risk factors, there is no way to accurately predict which aneurysms are at risk for rupture. Over the next 5 years we expect to see, further advancement in the arena of MR vessel wall imaging, and flow-modeling. We hope that this will help improve our predictive models.

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