Clinical Management of Cerebral Aneurysms

Yunyu Kuai
WLSA Shanghai Academy, Shanghai, China

Abstract. A number of people die every year because of aneurysms. Wide range of researches have been conducted into aneurysms, particularly for brain aneurysms. Due to the serious consequences of intracranial haemorrhage, there have been many new treatments including medication and surgical approaches developed in recent years, but at the same time there is still much room for technological improvement. As research has progressed, researchers have discovered that aneurysms are inextricably linked to inflammation and have proposed a number of medications to treat this condition. However, medication can only control aneurysms to a limited extent and is usually used as an adjunct to surgical treatment. This article summarizes the treatment of different aneurysms, as well as the prospect of surgical intervention and its future perspectives.

Keywords: Cerebral aneurysm, aspirin, ruptured aneurysm, embolization

1. Introduction
A cerebral aneurysm (CA) develops when a certain region becomes weak or thin on a cerebral artery that balloons or bulges and fills with blood. A bulging aneurysm can compress nerves or brain tissue [1]. Headache, unilateral orbital or retrobulbar discomfort, and ptosis are common symptoms of cerebral aneurysms, and some patients may also have hemiplegia, reduced consciousness, and other consequences such as subarachnoid haemorrhage and hydrocephalus. Aneurysms affect 2 to 5% of all Americans, with 15% having multiple aneurysms. Aneurysms that have not burst are more prevalent than those that have ruptured. 85% of them go undetected until they bleed. In Addition, aneurysms are more frequent in women and are often detected between the ages of 35 and 60 [2].

Ruptured aneurysms in other parts of the brain are less of a concern, however a ruptured aneurysm in the brain can directly affect brain function, resulting in insufficient blood supply and ischaemic and hypoxic encephalopathy, which can cause increased pressure on the limbs and brain and, in some cases, be fatal. Many people will prefer to operate early in order to limit the chance of a sudden brain hemorrhage, but having surgery does not imply that everything is certain. There will be post-operative symptoms of a brain aneurysm, such as hemorrhage, infarction, coil shedding, hydrocephalus, and limb impairment.

As introduced above, clinical management of cerebral aneurysm is very important. If patients do not receive timely therapeutic intervention in time, they may suffer from brain herniation, threatening their lives and health.
2. Unruptured and ruptured aneurysm

Around 2% of the general population has a brain aneurysm, with the majority of them asymptomatic and harmless (between 50% and 80%). While, spontaneous rupture of an aneurysm accounts for about 85% of nontraumatic subarachnoid hemorrhage (SAH), whose fatal rate ranges from 25% to 50% [3].

Ruptured cerebral aneurysms can cause subarachnoid haemorrhage, which is fatal and has a negative prognosis. At the same time, the aneurysm compresses the surrounding brain tissue and nerves, which can impair brain function. Furthermore, when a thrombus develops, it can break off in pieces under the influence of blood flow, obstructing the blood artery and causing the symptoms of cerebral infarction. A massive aneurysm may also cause blood flow in the blood arteries to slow, resulting in distal ischaemia and the symptoms of ischemic brain infarction. Ruptures most usually occur at the confluence of the anterior communicating artery and the anterior cerebral artery, the junction of the posterior communicating artery and the internal carotid artery, and the bifurcation of the middle cerebral artery [4]. Since the anterior and posterior communicating arteries are the most typical locations for aneurysm development, you should begin your search for a brain aneurysm on CT there. The majority of aneurysms form at the circle of Willis, the bifurcation of the middle cerebral artery (MCA), and the origin of the posterior inferior cerebellar artery (PICA) [5].

Diplopia, dilated pupils, and pain above and behind the eyes are all symptoms of an unruptured aneurysm. They may also have unexplainable headaches. However, if an aneurysm ruptures or a subarachnoid hemorrhage occurs, the patient will experience a terrible headache, which is commonly described as "the worst headache of a lifetime." At the same time, they will feel queasy and vomit, have seizures or rigors, and, more gravely, lose consciousness [6].

Smoking and high blood pressure are two key risk factors for aneurysm formation. Both of these risk factors, fortunately, are treatable. Other risk factors include genetic predisposition, drug use, heavy alcohol use, infection, and severe head trauma, with women being more likely than males to develop aneurysms [7]. There could be a link between brain aneurysms and hypertension as well. Congenital aneurysms and secondary aneurysms are the two forms of cerebral aneurysms. Aneurysms caused by congenital developmental defects are more common in teens, but they cannot be ruled out in older patients. Secondary aneurysms can develop as a result of hypertension or arteritis. If the aneurysm is caused by hypertension, it is the result of a long period of poor control of chronic hypertension, and the blood flow repeatedly flushes the walls of the blood vessels, resulting in lesions in the walls of the vessels and glassy changes in the elastic fibers inside, which then gradually bulge outwards under the blood flow, forming tiny aneurysms. Microaneurysms are the leading cause of cerebral haemorrhage. When blood pressure changes dramatically, the capillaries enlarge to some amount and can easily burst, resulting in cerebral haemorrhage [8].

3. Major mechanism of CA: inflammation

Recent research on the inflammatory mechanism of cerebral aneurysm has revealed that inflammatory cells infiltrate and destroy the elastic and collagen fibers of the cerebral artery wall, resulting in the disease's progression. The main cells involved are macrophages, where monocyte chemotactic protein-1 (MCP-1) regulates the expression of pro-inflammatory genes such as MCP-1, and nuclear factor-xb (NF-B), which transcriptionally regulates the expression of pro-inflammatory genes the same as MCP-1, and matrix metalloproteinases (MMPs), particularly MMP-9, are abnormally highly expressed [9]. NF-κB is involved in the inflammatory response and plays a regulatory role. Many researchers have shown that NF-κB has a role in promoting the expression of inflammatory genes in the inflammatory response, and that NF-κB can be transcribed and released by cellular signals when cells are stimulated by a variety of factors[10]. Recent studies have reported that NF-κB is closely associated with the development of cerebral aneurysms, causing macrophages to accumulate in the aneurysm wall and degrade the extracellular matrix by initiating pro-inflammatory factors [11].

While MCP-1 functions as an initiator, causing mononuclear macrophages to collect and stick to the arterial wall, active chemicals such as MMPs release elastic and collagen fibers that can alert the arterial wall, triggering restrictive dilation of the artery. NF-B regulates the transcription of
pro-inflammatory genes such as MCP-1 [12]. This pathological alteration damages the vessel wall, resulting in degenerative vascular elasticity. The immune inflammatory response plays critical role in the genesis and evolution of cerebral aneurysms, with the main mechanism being the activation of endothelial cells by inflammatory substances. Both burst and unruptured cerebral aneurysms have inflammatory cell infiltration in the wall, indicating an inflammatory response prior to aneurysm rupture [13].

Moreover, MPP-9 is a pro-inflammatory protease with high sensitivity to a wide range of pro-inflammatory stimuli. Activated MMP-9 can degrade a variety of extracellular matrix, aiding the formation, progression, and rupture of cerebral aneurysms. It has been proposed that NF-B regulates MMP-9 in the development of cerebral aneurysms [14]. MMP-9 expression was higher in the walls of cerebral aneurysms in individuals with cerebral aneurysms than in those without cerebral aneurysms, implying that elevated levels of MMP-9 expression may be a substantial contribution to the formation and progression of cerebral aneurysmal illness. MMP secretion can be stimulated by inflammatory cell infiltration, and alterations in MMP-9 expression are particularly noticeable. MMP-9 expression that is abnormally high can cause the degradation of elastic and collagen fibers in the cerebral artery wall, which eventually promotes the development of disease [15].

![Figure 1. Aspirin in the pathogenesis of cerebral aneurysms.](image)

4. Clinical management of UCA

4.1. Medication of unruptured aneurysms

In summary, intracranial aneurysms are currently regarded as lesions of the vascular wall mediated by a chronic inflammatory response, with pathological changes involving multiple cellular and cytokine interactions that provide targets for drug intervention. Recent studies suggest that intracranial aneurysms that do not meet the indications for surgery may be manageable with medication, for example by Aspirin, Statins and Glucose-lowering drugs.

4.1.1. Aspirin-antipyretic, analgesic and anti-inflammatory. Aspirin is a nonsteroidal anti-inflammatory medication that has antipyretic and anti-inflammatory properties due to its suppression of cyclooxygenase 2. It has therapeutic potential for cerebral aneurysms and is one of the most researched medications in this field. Several clinical investigations have looked into aspirin's potential therapeutic role in cerebral aneurysms. Aspirin administration frequency has been
demonstrated to be adversely associated with intracranial aneurysm rupture, and aspirin may be taken alone to prevent intracranial aneurysm dilation [16]. A cross-sectional study of 110 people with metabolic syndrome was conducted. Blood samples were collected after one week of taking 100 mg of aspirin daily. The frequency of aspirin resistance was determined using a platelet function analyzer (PFA-100). Endothelial function, carotid intima media thickness, and the presence of plaques in the carotid arteries were analyzed for subclinical atherosclerosis, and inflammatory marker levels were investigated as risk factors for aspirin resistance. A maximum carotid intima media thickness of \( > 0.9 \text{ mm} \) and/or the presence of carotid atheroma were used to identify the presence of subclinical atherosclerosis [17]. Although studies have shown that aspirin could indeed help delay the development of intracranial aneurysms and has great therapeutic potential, more prospective studies are needed to assess the duration of aspirin administration, dose range, and population indication to provide more evidence for clinical practitioners (Figure 1).

4.1.2. Statins-lowering serum cholesterol. Statins, which block hydroxymethylglutaryl coenzyme A reductase, are extensively used in clinical practice to decrease serum cholesterol and prevent stroke and cardiovascular disease. Statins are used to prevent the progression of intracranial aneurysms by a different mechanism than cholesterol reduction, mostly through an anti-inflammatory impact at the artery wall. Statin therapy often lowers the relative risk of cardiovascular disease by 24-37\% regardless of age, gender, past history of CHD, or other co-morbid diseases [18]. In animal studies on rats with aneurysms, the amount of NF-B activation in the aneurysms of rats on statins reduced, as did the expression of MMPs, IL-1, MCP-1, VCAM-1, and other factors that promote the advancement of intracranial aneurysms, decreasing the progression of intracranial aneurysms. However, due to individual variances, such as varied blood concentrations, the dosage of these medications requires more investigation [19].

4.1.3. Glucose-lowering drugs-inhibition of intracranial aneurysm dilation. Glucose-lowering medications may decrease the dilatation of cerebral aneurysms. Anegliptin is a dipeptidyl peptidase 4 inhibitor hypoglycemic drug that has recently been demonstrated to activate extracellular signal-regulated kinase 5, which suppresses macrophage inflammatory response by decreasing nuclear factor B activation. Another regularly used hypoglycemic medication, pioglitazone, has been demonstrated in animal trials to suppress inflammatory markers such as MCP-1, IL-1, and IL-6 at the aneurysm lesion as well as macrophage infiltration, hence avoiding intracranial aneurysm rupture [20]. Glucagon-like peptide-1 agonists have anti-inflammatory as well as hypoglycemic properties, although their impact in intracranial aneurysms is unknown. In conclusion, hypoglycemic medications may have therapeutic effects on intracranial aneurysms, but further fundamental tests and animal studies, as well as clinical trials, are required to uncover their mechanism of action.

4.2. Surgery of unruptured aneurysms

CA is produced by an abnormal protrusion of the blood vessel walls of the intracranial arteries and is prone to rupture and hemorrhage. There are no specific drugs that can completely inhibit the rupture of an aneurysm, so conservative treatment with drugs is not usually recommended after the diagnosis of an intracranial aneurysm. Surgical intervention, such as microsurgical clipping or endovascular embolization, is usually used to treat it as soon as possible. Patients who receive timely surgical therapy before the aneurysm ruptures have a better chance of recovering completely.

4.2.1. Microvascular clipping. For brain aneurysms, microsurgical clipping is another well-established approach. It was first developed by a Johns Hopkins surgeon in the 1930s, and doctors have fine-tuned the technique over years. A neurosurgeon team enters the brain through a small incision in this specialized surgery. A titanium clip is placed over the aneurysm’s neck by the neurosurgeon. The clip preserves normal blood vessels and at the same time stops extra blood from getting into the aneurysm. It also greatly lowers the risk of bleeding in the brain. Today, with the help of intraoperative angiography, doctors can assess the effectiveness before and after surgery and ensure a successful result. And neurosurgeons today are able to make a even smaller opening in the skull,
making less scarring. After clipping, chances of an aneurysm recurring become much smaller, so that it requires less follow-up testing. However, it often requires a recovery of at least four to six weeks [2]. In one study, the coiling group had a higher short-term mortality (38% vs. 15%, P = 0.015). The clipping group had a considerably higher incidence of delayed cerebral ischemia and intracranial infection than the coiling group [21].

4.2.2. Endovascular coiling. The purpose of endovascular coiling, known as cardiovascular disease coil embolization or simply "coiling," is to seal off the cardiovascular disease by inserting soft platinum coils into the aneurysm via the catheter. By covering the artery's faint bulging allotment, a blood clot around the coil will be built, dramatically reducing the danger of shatter. Coil embolization for cardiovascular disease was possible in both ruptured and unruptured aneurysms. Coil embolization is the most commonly used approach for brain aneurysms considering that open surgery often comes with a significant risk.

Factors should be considered when choosing a patient as candidate for coil treatment are the patient's age and health status along with the location, size and shape of the aneurysm. The arrangement is conducted below general anesthesia and the anesthesia squad is additionally introduced to closely monitor blood pressure, heart rate and rhythm moreover blood oxygenation whilst the embolization procedure. Minimally invasive coil embolization allows for the treatment of previously inoperable brain aneurysms. This arrangement is less invasive and needs remarkably less recovery time than begin surgery for cardiovascular disease repair. While the shortcomings of it is the likelihood of recurrence proved by MRA or cerebral angiography. The interventional neuroradiology team will plan the follow-up tests. More than 80% of aneurysms treated with coil embolization have shown long-term success. Only approximately 10 to 15% of aneurysms necessitate coil resection. Only a tiny proportion of individuals may need familiar initiate surgery [22]. Similar to any invasive procedure in the cerebral blood veins, there is a chance of death, stroke, and also less serious problems such as infection, hemorrhage, allergic response, and kidney failure. There is a 5-9% chance of having a stroke, having a heart attack, or dying. Because of technological advancements like smaller stents and soft balloons, most aneurysms are now amenable to coil embolization. Consequently, large aneurysms accompanied with wide necks continue to be an unsolved problem.

4.2.3. Flow diversion devices. Until stents are applied, there are a number of aneurysms that cannot be resolved by minimally invasive interventional methods. The spring coil has to be inserted into the vascular bubble, as full as possible, in order to achieve treatment. Some vascular blisters have a closed opening and the spring coil can be placed securely in the aneurysm without falling out; this does not require a stent and is feasible with a spring coil alone. The remaining vascular vesicles are open. They are unable to be implanted and will fall out, obstructing the usual vessel. The doctors attempted to solve the problem but were unable to do so optimally and were forced to resort to open surgery. Before Previously, the recurrence rate of aneurysms treated with non-stent interventional procedures was as high as 30%, implying that two or three patients out of every ten would recur. In other words, two or three patients out of every ten will have a recurrence. The use of stents can lower the recurrence rate to 10% [23].

Flow diversion is a tool that interventional neuroradiologists are increasingly employing. Since they were initially released roughly ten years ago, there has been a considerable shift in how these devices are used. Clinicians are treating increasingly complex patients and employing them more frequently as their practice grows. Similar devices have now been successfully deployed distal to the Willis circle in a manner similar to this. Despite the fact that technology is becoming obsolete, significant progress is being made. The Silk Vista Baby and other contemporary devices, such as surface coatings that require only one anti-platelet agent and totally transparent DFT devices, can be implanted using 0.17-inch microcatheters. As technology advances, remote aneurysms and burst aneurysms may become more curable. With the use of stents, the recurrence rate of aneurysms has been considerably reduced [24].
4.3. Other treatments
Flow diversion has become an indispensable tool in the arsenal of the interventional neuroradiologist. There has already been a significant shift in their utilization since their launch roughly ten years ago. With increasing experience, practitioners are using them more frequently and managing more complex situations. Similarly, similar devices have now been used distally to the Willis circle with good outcomes. Even if the technology is no longer cutting-edge, significant breakthroughs are still being produced. Newer devices, such as the Silk View Baby [25], can be deployed over 0.17 poke microcatheters, devices with surface coatings that require only one antiplatelet agent, and totally visible DFT devices. These technological advancements are making the prospective treatment of distant aneurysms and burst aneurysms more accessible to sail diversion, which has previously been shown to provide cardiovascular disease occlusion comparable to clipping.

Recently, there have been several advancements in the field of sail diversion, including the aforementioned novel devices as well as newly developed coatings that limit stent thrombosis. The goal of this research topic is to introduce the vast majority of current advances on these topics in such a way that readers are up to date on all of the most recent technological advancements made, as well as to provide patients and clinicians with the vast majority of up-to-date information on safety and efficacy.

4.4. Prognosis of ruptured aneurysm
Severe complications may occur as a result of a burst aneurysm or following surgery. An aneurysm that has ruptured may rupture again before it can be treated, causing further brain hemorrhage and more damage or death. An aneurysm can burst and flow into the space between the skull and the brain (subarachnoid haemorrhage) or into brain tissue in rare cases (intracerebral haemorrhage). These are all types of strokes known as haemorrhagic strokes. Bleeding into the brain can produce a variety of symptoms, ranging from a minor headache to severe brain damage and even death. A subarachnoid hemorrhage can also induce hydrocephalus. Too much cerebrospinal fluid in the brain increases intracranial pressure, which can result in irreversible brain damage or death. Because the blood blocks the normal flow of cerebrospinal fluid, hydrocephalus frequently arises following a subarachnoid hemorrhage. If the increasing pressure in the head is not addressed, it might result in coma or death.

After a subarachnoid hemorrhage, the arteries in the brain constrict and impede blood flow to important parts of the brain. Vasospasm can lead to an ischemic stroke, which is a stroke caused by insufficient blood supply to areas of the brain. Endovascular embolization or surgical clamping only minimizes the likelihood of re-rupture and bleeding, but does not repair the bleeding caused by a ruptured aneurysm. Anti-cerebral vasospasm and neurotropic therapy are necessary postoperatively.

5. Conclusion
Introduction of cerebral aneurysm from various angles, and various aneurysm intervention approaches are detailed. Especially given that the mechanism of aneurysms is heavily influenced by inflammation. In terms of surgical intervention, various common procedures are discussed, and thanks to technological advancements, the likelihood of subsequent rupture following surgery is considerably decreased.

Endovascular methods and materials for aneurysm therapy are still advancing at a rapid rate at this point. Trans-luminal vascular tissue engineering, a novel approach based on bioengineering, molecular biology, and cell biology, is now being included into the vascular therapy strategy for intracranial aneurysms. It entails inserting proteins, genes, vascular smooth muscle cells, vascular endothelial cells, extracellular matrix, or cytokines prepared in vitro into the aneurysm lumen using conventional catheter techniques, with spring coils and stents serving as mechanical carriers and adenovirus, retrovirus, or biodegradable polymer materials serving as biological carriers, to allow the aneurysm to heal anatomically. Although there are still technological obstacles, this hypothesis is backed by a large body of experimental evidence. In terms of the future of endovascular therapeutic devices, it may be realistic to progress from delivery system improvements to the integration of endoscopy with
microcatheters and microguidewires, endovascular navigation, and delivery system artificial intelligence. Endovascular therapy is likely to become the preferred method of treating cerebral aneurysms as embolization materials and procedures improve.

Reference