**Supplemental Material**

Spontaneous subarachnoid Hemorrhage (SAH) is a severe subtype of stroke with an incidence between 1 and 27 per 100,000 person-years. The incidence of spontaneous SAH varied by region and racial. It was higher in women and increased with aging [1]. The annual incidence of spontaneous SAH in Chinese population is also various among different studies. The incidence is generally both higher in north 6.2 per 100,000 person-years in Baotou, Inner Mongolia [2]. In the central and south region of China, the incidence is relatively low, with 2.2 per 100,000 person-years (95% CI: 1.2~5.4) in Changsha, 1.1 per 100,000 person-years in Shanghai[3], 1.2 per 100,000 person-years in Shunde, Guangdong Province[4] and 3.02-4.45 per 100,000 person-years in Chengdu[5]. However, it is as high as 6.25 per 100,000 person-years in Taiwan [6] and as low as 1.6 per 100,000 person-years (95% CI:0.8~4.1) in Beijing [3]. There were few studies on the prevalence of SAH till now. Only a national study in South Korea reported that the prevalence of SAH was 19.8~ 21.0 per 100,000 person-years [7].

## Section 1 Diagnosis and Severity Assessment of SAH

### 1.Clinical and imaging diagnosis of SAH

Spontaneous subarachnoid hemorrhage is a serious and life-threatening medical condition which commonly presents with an acute headache. The

extremely sudden and immediately reaching maximal intensity thunderclap headaches should be differential diagnosed with SAH [8]. Approximately 80% of patients with SAH describe the pain as "the worst headache of life" [8]. Patients with SAH may or may not be accompanied by nausea, vomiting, stiff neck, brief loss of consciousness, focal neurological signs and so on. A retrospective study of 109 patients with SAH indicated that 55% patients present with brief loss of consciousness, 77% with nausea or vomiting, and 35% with nuchal rigidity [9]. A multicenter cohort study which enrolled 2131 patients indicated that among people at any age of 40 years or older, neck pain or stiffness, witness of loss of consciousness, or onset during exertion adding thunderclap headache and limited neck flexion on examination are reliable decision rules to rule out SAH at a sensitivity of 100% and a specificity of 15.3% [10]. This finding was supported by another prospective observational study, and they also added that occipital location, stabbing quality, presence of meningism were characteristics [11]. The Ottawa headache rule is a clinical decision tool which was developed to help identify patients presenting to the ED with acute non-traumatic headache who require investigation to rule out subarachnoid hemorrhage (Supplemental Table1) [11]. Moreover, the severe of headache was associated nonlinearly with the severity of SAH [12].

Computed tomography (CT) is the first-line choice for SAH diagnosis. A prospective cohort study which enrolled 3,132 patients with a new acute headache, was reported that the sensitivity of CT for SAH in those whose

peaking pain within an hour was 92.9% and specificity was 100%. If patients as such were scanned within 6 hours of headache onset, yielding a sensitivity and specificity of 100% [13]. A retrospective study of 499 patients indicated that CT scanning have a sensitivity of 99.7% within 1 to 5 days after SAH [14], but the sensitivity of CT diagnosis decreased sharply after 5-7 days. Therefore, if SAH is suspected, CT scan should be performed as soon as possible.

If the CT result is negative, the diagnosis may be assisted by diagnostic lumbar puncture [15]. If red blood cells and yellowing are found in the cerebrospinal fluid (CSF), the diagnosis of subarachnoid hemorrhage can be supported. If only fresh blood is found in the cerebrospinal fluid, it needs to be differentiated from trauma related to lumbar puncture. When proceeding lumbar puncture, three tubes of cerebrospinal fluid need to be continuously collected. If the three tubes of CSF all showed consistent blood or xanthochromia, the diagnosis of subarachnoid hemorrhage was supported. If only the first tube is red or pink, the color of the latter two tubes gradually fades, lumbar puncture wounds should be considered [15-16].

## Recommendations

1. **Acute onset of severe headache is one of the initial and major symptoms. The Ottawa headache tool may be useful to differentiate the diagnoses (Class I; Level of Evidence B).**
2. **Noncontrast head computer tomography (CT) should be the initial imaging study for patients with suspected** spontaneous **SAH, if non-diagnostic, lumbar**

**puncture should be considered (Class IIa ; Level of Evidence B).**

## 2 Etiology of SAH

Excluding injuries and iatrogenic factors, common causes of spontaneous SAH include aneurysms, cavernous hemangioma, venous thrombosis, arteriovenous malformations and cerebral arteriovenous fistula [17], cerebral amyloid angiopathy [18-20], tumor bleeding, special vasculitis / encephalitis [19], abnormal blood coagulation[21], and rare causes such as postpartum eclampsia, reversible cerebral vasoconstriction syndrome[18], etc. According to the SAH site showed on cranial CT scan, SAH is classified into convex SAH and non-convex SAH. The former is more common in venous system embolism, venous sinus thrombosis and cerebral amyloid angiopathy [19-20], while the latter more common in aneurysms.

*(a) Aneurysmal SAH*

According to the characteristics of SAH distribution, intracranial artery examination should be highlighted.

1. CTA

   Computed Tomography Angiography (CTA) can be used in the detection of aneurysms. It showed the relationship between aneurysm and bony structure, with high sensitivity >77%, and specificity >79% [21]. The detection rate of CTA on aneurysms is affected by many factors, such as

aneurysm size, aneurysm location, CT imaging equipment, scanning parameters and CTA post-processing techniques. CTA has a sensitivity of 95%-100% for aneurysms ≥5mm, but when the diameter of an aneurysm is <5mm, the sensitivity decreases to 64%-83% [22-23]. Previous studies have suggested that aneurysms <3mm in diameter is unreliably demonstrated on CTA [24-25]. It has been reported that the sensitivity of CTA for aneurysms with diameter <4mm is 92.3%, and when the diameter of aneurysm is ≥4mm, the sensitivity increased to 100% [26]. Li et al found that 64-row spiral CTA detection of aneurysms with a long diameter > 3 mm can reach the sensitivity of 93.7% ~ 96.8% [27]. With the advancement of CT imaging technology, the detection rate of CTA for microaneurysms has been significantly improved. The subtraction CTA technique can display the aneurysm better than the conventional CTA by avoiding the interference of bony structure adjacent to the aneurysm and improve the detection rate of the aneurysm [28]. Therefore, CTA is recommended as a primary examination tool for aneurysm detection [23-30]. In addition, 4D-CTA allows for a good temporal and spatial resolution at acceptable radiation doses [29]. Although some angio-architectural details were missed or misinterpreted when compared to DSA, the accuracy of 4D-CTA assessment is sufficient to meet basic clinical needs and some specific case [29-30]. CTA is suitable for the detection of aneurysms with the advantages of economy, short imaging time and wide application. Compared with DSA, CTA has certain advantages

in identifying the aneurysm wall calcification, intraluminal thrombus and the relationship between aneurysm and bone structure.

Besides, CTA examination can also be used in detecting arteriovenous malformation [30]. Compared with digital subtraction angiography (DSA), the sensitivity of CTA for arteriovenous malformation is 90%, while the sensitivity of 1.5T TOF MRA is 74% [29-30]. In general, CTA should be considered as an emergency initial test for aneurysm.

2. MRI and MRA

Magnetic resonance imaging (MRI) is the main technique of assisting in the diagnosis of SAH. Fluid-attenuated inversion recovery (FLAIR) imaging, Proton Density Imaging, Diffusion Weighted Imaging (DWI), gradient echo sequences or susceptibility weighted imaging (SWI) are very sensitive to heme display [31]. Magnetic resonance angiography (MRA) can be divided into non-contrast MRA, such as Time-of-Flight (TOF) MRA, and contrast-enhancement MRA [32,33]. 3D TOF MRA is suitable for pregnant women and patients who cannot use contrast agents for does not require contrast agents and has no ionizing radiation. However, its shortcoming is poor sensitivity [34] compared to MRA, CTA and DSA [17,34-35]. Although it has been reported that the sensitivity of MRA for aneurysms can reach 70% to 98% [36], there remains limitations of determining the relationship between the aneurysm neck and the associated blood vessels.

3. DSA

Despite the rapid development of CTA and MRA techniques, DSA remains the "gold standard" for the diagnosis of intracranial aneurysms [35-37]. However, DSA is an invasive inspection with high costs. The 3D DSA can stereoscopically display the size, location, and relationship of the aneurysm to surrounding blood vessels. Compared with traditional 2D DSA, it has the advantage of detecting microaneurysms. It is possible that the first DSA assessment showed false negatives. For patients who have a negative baseline assessment, DSA may be repeated. The timing of the repeat DSA could be from 1 to 6 weeks after the initial DSA and the specific time should be judged according to the experience of the physician [38-39]. Recently, a meta-analysis showed that undertaking a DSA after a negative CTA may not add any further diagnostic value in patients with perimesencephalic SAH and may lead to net harm [40]. As DSA has certain risks and high costs, the necessity of repeat checking should be carefully considered according to individualized therapy.

(B) non-aneurysmal SAH

For convex SAH, cerebral vascular amyloidosis and venous embolism or vascular malformation should be carefully identified when excluding aneurysmal SAH.

1. 3D TOF MRA

The drainage vein on 3D TOF MRA imaging emits a high signal, but studies comparing 3D TOF MRA and DSA show that only 65% of the blood

supply artery and 72% of the drainage vein can be identified on the MRA [41], the sensitivity is relatively low [42-44].

2. SWI

The principle of SWI is based on the deposition of hemosiderin, thus it can display low-signal drainage veins that cannot be shown on 3D TOF MRA images [45]. In addition, for patients with suspected cerebrovascular amyloidosis, SWI is able to detect cortex microbleeds in the brain [17]. Therefore, SWI is sensitive to cerebral vascular amyloidosis and venous thrombosis and venous malformation, but may not be sensitive to cerebral arteriovenous malformations [19,45-47].

3. DSA

DSA is the most reliable and important method for diagnosing cerebral arteriovenous malformation. It is also the reference standard for diagnosis of reversible cerebral vasoconstriction syndrome and rare cortical vein embolism. Its unsurpassed spatial and temporal resolution allow it to clearly delineate the location, depth, size of the lesion, the relationship between the feeding artery and the trunk, and the number and distribution of the drainage vein [46]. In addition, compared with 2D DSA, 3D DSA is more detailed in assessing vascular structure and can more accurately display the spatial structure of arteriovenous malformation/arteriovenous fistula [48].

## Recommendations

1. **CT angiography (CTA) is essential for finding the etiology of SAH, therefore each**

**stroke center can perform CTA 24 hours/7 days. (Class I; Level of Evidence B). Contrast magnetic resonance angiography (MRA) and 3D time of flight (TOF) MRA are optional choices for patients who are ineligible to have a CTA. For suspected arteriovenous malformation (AVM) that causes SAH, susceptibility weighted imaging (SWI) should be performed (Class IIa, Level of Evidence B).**

2. **MRI (with FLAIR, DWI, SWI or T2*) is a reasonable tool to explore the etiology of SAH. Lumbar puncture should be performed in patients with a negative CT of head. (Class IIa, Level of Evidence C).**
3. **Digital subtraction angiography (DSA) can be used as a standard reference for discovering the etiology of SAH, and a tool to further evaluate the treatment, such as endovascular treatment or surgery (Class IIa, Level of Evidence B). If the initial DSA is negative, DSA might not essential to repeat within 1 to 6 weeks，if CTA is available (Class IIb, Level of Evidence C).**

## 3 Flowchart of SAH diagnose（Figure1）

## 4 The Severity Assessment of SAH

In order to assess the severity of SAH, the Hunt-Hess scale and the World Federation of Neurosurgical Societies (WFNS) grading scale (Supplemental Table 2 and Supplemental Table 3) are widely used. Among them, WFNS grading scale is the most classic method characterized as simple, reliable and effective. The higher the WFNS graded, the more severe the condition is. The Hunt-Hess scale is mainly used to classify patients with subarachnoid

hemorrhage with aneurysm to estimate the risk of surgery and the prognosis of patients [48].

Based on the imaging findings of SAH patients, further assessment method can be performed such as Fisher grading (Supplemental Table 4)[49], modified Fisher grading (Supplemental Table 5)[50], Hijdra scores (quantitative scoring of 10 parts of subarachnoid hemorrhage including frontal interhemispheric fissure, left lateral sylvian fissure, right lateral sylvian fissure, left basal sylvian fissure, right basal sylvian fissure, left suprasellar cistern, right suprasellar cistern, left ambient cistern, right ambient cistern, quadrigeminal cistern; 0 points Indicates no bleeding, 1 point indicates a small amount of bleeding, 2 points indicates moderate bleeding, 3 points indicates massive bleeding, total score is 30 points)[51], Claassen grading (Supplemental Table 6) and so on[52]. These scores graded high are mainly associated with delayed cerebral infarction (DCI) or cerebral vasospasm (CVS) [51-52]. However, there is currently not enough evidence to recommend which scale is better since the interobserver consistency among scales was not satisfied [53]. The Fisher grading and modified Fisher grading based on rough imaging results may predict risk of DCI and CVS [52], while the Barrow Neurological Institution Scoring (BNI) score and modified Fisher scale might be able to indicate the risk of symptomatic CVS (Supplemental Table 7 and Supplemental Table 8) [54-55].

**Recommendations**

1. **The initial clinical severity and prognosis of SAH should be evaluated by the use of clinical grading system such as the Hunt and Hess scale, or WNFS scale. (Class I; Level of Evidence B)**
2. **The risk of DCI and CVS in SAH should be evaluated by the use of relatively simple radiographic grading scale, such as the Fisher grading scale or the modified Fisher grading scale. (Class IIb; Level of Evidence B)**

## Section 2 SAH early management

Acute intensive care should be considered for all SAH patients. Acute phase monitoring and symptomatic treatment of complications. Different level of stroke centers needs to focus on various key elements. For comprehensive stroke center, more criteria, emphasizing on intervention, neurosurgery and multidiscipline team, were measured for stroke care quality and its improvement process. In general, the flowchart of SAH acute management is shown in Figure 2.

### 1. Designation of stroke center and transfer

Stroke systems of care integrate regional stroke facilities, including primary and comprehensive stroke centers[56-57], EMS system[58], public and national health commission and agents[59-60]. The goals of creating stroke systems of

care include acute stroke treatment, stroke prevention and public education. The details were described in another section of CSA guidelines.

For SAH patients, the data highlighting that those stroke center treating more SAH cases had lower mortality and better clinical outcome among eight large-scaled trials [56-63]. Another nationwide retrospective cohort analysis reported the SAH treatment in a high-volume center was associated with low mortality (OR 0.82, 95%CI 0.72-0.95; P<.01) and better functional outcome (OR, 1.16; 95%CI 1.04-1.28; P<.01) [56] and a meta-analysis confirmed this findings [64]. A retrospective study showed that initiation of neuro-intensivist co-management was associated with ICU stay reduction (average length of stay 12.4d vs. 10.9d, p=0.02), was unlikely associated with mortality [65].

**Recommendations:**

1. **Patients with severe SAH should be transferred to an experienced comprehensive hospital for further intervention in order to reduce mortality. Severe SAH is defined as having an aneurysm, more than 3 points on Hess-Hunt Scale or a grade of IV~V on WFNS (Class IIa, Level of Evidence B).**
2. **All stroke centers should operate a CT scanner 24hour*7days. Comprehensive stroke center should have a team of neurosurgeons, neuro- interventionalists, and neuro-intensivists, which is essential to provide high quality of care (Class IIa, Level of Evidence B).**

**2. Blood Pressure Management**

In SAH acute management, five large retrospective studies confirmed that hypertension was one of major risk factors of rebleeding which leaded to worsening [66-69]. The risk of hypertension and rebleeding is positively correlated, and systolic blood pressure greater than 160 mm Hg is an independent risk factor for aneurysm rebleeding, and unstable blood pressure also increases the risk of rebleeding [66,67]. Therefore, blood pressure be maintained as less than 160mmHg is reasonable. Recently, a cohort study also supported that there was a trend of stroke risk decreasing of BP control (OR 2.1 in 1976-1978 and 1.5 in 2003-2015)[70].

On the one hand, three large RCTs showed that BP lowering agent should be administrated in acute phase [71-73]. Among them, intravenous nicardipine is more rapid and stable [74], while bonus might be not. Intensive BP management in acute phase might bring the risk reduction of rebleeding and slightly increasing the rate of delayed cerebral infarction [67,71,72]. On the other hand, A large sample retrospective study also supported that patients with hypotension had a poor prognosis and high mortality [69]. In INTERACT2 trial SAH extension subgroup, SBP target as 140mmHg was feasible [75]. In addition, handling BP too strictly, such as continuous intra-arterial nimodipine might be inappropriate since the BP variability is a novel risk factor [69,76].

Also, daily activities like defecation/micturition, brushing teeth/washing face/dressing, eating/drinking, and taking a bath were associated with a

Valsalva maneuver that results in sudden pressure changes across the aneurysmal wall precipitating aneurysmal rupture SAH patients [77]. Therefore, patients should avoid nervous and stress.

**Recommend:**

1. **Intensive blood pressure (BP) management in early phase of SAH is recommended. SBP is reasonable to be kept below 160mmHg and reduce variations. (Class IIa, Level of Evidence B). However, dropping SBP too low (<130mmHg) or having high variability might be harmful (Class III, Level of Evidence B).**
2. **BP lowering agent should be administrated intravenously during the acute phase. Calcium channel blockers such as nicardipine or beta-blockers such as labetalol are appropriate agents to reach and maintain the target BP range (Class I, Level of Evidence B). However, hypotension can be induced from continuous intra-arterial nimodipine infusion. (Class IIb, Level of Evidence B)**
3. **SAH patients should be kept calm and avoid nervous conditions or stress. Constipation should be prevented. Bathing alone should be avoided. (Class I, Level of Evidence C)**

## 3. blood glucose management

A meta-analysis of blood glucose management after subarachnoid hemorrhage, including 8 studies, reported that hyperglycemia at baseline was

a major risk factor of poor prognosis [78]. Another retrospective study confirmed this finding and added that it was also associated with the higher rate of DCI [79]. Also, diabetes mellites also was also associated with risk of CVS [80]. Therefore, blood glucose level can be used as one of the indicators for predicting prognosis. However, strictly blood glucose control did not change the patient's mortality rate since hypoglycemia was also associated with higher mortality rate [81]. Therefore, SAH patients with hyperglycemia is more likely having a poor prognosis, high mortality and DCI. However, there is currently inconclusive evidence that what range of glucose level is best.

**Recommendation**

1. **Hyperglycemia in SAH patients is associated with poor prognosis and increased mortality (Class IIb, Level of Evidence A). However, aggressive control of hyperglycemia may not change the clinical outcome. Hypoglycemia should be avoided (Class IIb, Level of Evidence B).**

## 4. Headache management

Thunderclap headache is the initial and most common symptom in SAH patients [82]. Headache would likely continuously exist if the patients with risk of CVS and rebleeding. Headache management focuses on the rebleeding prevention [83]. Unusually, SAH due acute CSF hypotension was need to be differential diagnosed [84].

**Recommendation:**

1. **Treatment should focus on CVS and rebleeding prevention. For patients with severe headache, comprehensive management including headache relief needs to be considered (Class I, Level of Evidence C).**

## 5. Rebleeding and hemostasis treatment

Due to the high risk of rebleeding in first-two weeks after aSAH, the early management for rebleeding prevention is of importance, in order to have a better clinical outcome. For aSAH patients, the invasive interventions including endovascular treatment, aneurysm clipping surgery as well as hybrid operation are preferred to reduce the risk of rebleeding. Besides, medical treatment is preferred for patients who are aneurysm-negative.

### 5.1 Surgical treatment

For most patients with aneurysms, MDT treatment is necessary in the acute stage. Neurosurgeons should consider if the intracranial aneurysm suit to be clipped, in order to prevent re-bleeding. Take the advantage of surgery, giant aneurysms and poor-grade SAH were prefer urgent surgery [85-90]. Other techniques options such as aneurysm clipping, aneurysm isolation combined with bypass surgery, aneurysm wrapping and parent artery occlusion can be selected according to the shape and location of the aneurysm[85,91,92]. The

Barrow Ruptured Aneurysm Trial, (BRAT) showed that surgical treatment of intracranial aneurysms had a high rate of complete occlusion as a major complication [85]. Two international long-term observational studies showed that the recurrence rate and rebleeding rate of surgical treatment are relatively low, compared with endovascular treatmentendovascular treatment [93,94]. In a national study, both coil embolization and microsurgical clipping were preferable options for aneurysmal SAH patients [95].

In addition, craniotomy has an advantage of good vision and convenient operation. It has operational advantages for the middle cerebral artery, periorbital artery, or aneurysm involved with branch vessels [54,87,89].

However, there are many limiting factors in surgical treatment. As the aneurysm is deep location, large size, severe neck calcification, as well as heavily adhesion to neighboring structures, all of which affect the decision-making [96,97].

5.2 Endovascular treatment

Endovascular treatment is a method to coiled and embolize the aneurysm as well as rebuild the parent artery (or occlude malformation) with the guidance of CTA [98]. International Aneurysm Test for Subarachnoid Hemorrhage Trial showed that endovascular treatment has a significantly lower complication rate and mortality rate compared with surgical treatment (8% vs 19%, 24% vs 31%) [99]. Besides, the risk of postoperative epilepsy and cognitive impairment are

also relatively low [99]. With the progression of treatment strategy as well as the novel devices, endovascular treatment of intracranial aneurysms becomes important and as preferable. Novel techniques including Stent-assisted coiling, using baby stenting following balloon-assisted coiling, dual stent techniques, pipeline embolization device, and so on were utility and more RCT trials are needed in future [100-103]. Developing flow diverter devices were complex due to its competing results. The Surpass trial showed that the Surpass flow diverter had a safety profile that is comparable with that of stent-assisted coil embolization [104], while the FIAT trial was terminated due to safety concerns[105]. It is currently consensus that patients with higher grade of Hunt-Hess scale (Grade 4-5), elder (> 70 years old) might be more suitable for endovascular treatment but also lacking of decent technical evidence[85].

Complications are also need to be noted. Intraprocedural rupture (IPR) is a well-known complication of intracranial aneurysm treatment. CARAT showed that patients with coronary artery disease and initial lower Hunt and Hess Grade were independent predictors of IPR [106]. The recurrence rate of aneurysm after endovascular treatment is high to 38.5% [93,107] . While in recent study, there were several reports of complications of endovascular treatment for intracranial aneurysms as high as 7.7% -15.38% [93,94,107]. Generally, the early survival advantage of endovascular treatment was maintained for up to 7 years and was significant [107]. The risk of epilepsy was substantially lower in patients allocated to endovascular treatment, but the risk of late rebleeding

was higher [107]. The application of newly embolize devices reduce the recurrence rate and complications but still lacking of evidence from randomized control study[104,105,108,109].

Some stroke center has hybrid operating room, which allows simultaneous surgical and endovascular treatment to complement the two treatments. The therapeutic effect of the method requires the support of relevant clinical research evidence.

## Recommendations

1. **For most SAH patients with a ruptured aneurysm, endovascular or surgical treatment should be considered as soon as possible (less than 72h), in order to reduce the risk of rebleeding. (Class I, Level of Evidence B).**
2. **The interventional or surgical treatment plan should be discussed and determined by multidisciplinary team, by experienced neurosurgeons and neuro-interventionalists (Class I, Level of Evidence C).**
3. **For patients with an aneurysm suitable for either interventional or microsurgical treatment, endovascular treatment is preferred (Class I, Level of Evidence A). For SAH patients older than 70 and with a Hunt-Hess scale between 4-5, endovascular treatment is preferred (Class IIa, Level of Evidence B).**

5.3 Medicine

A multicenter randomized study that tranexamic acid reduced early rebleeding risk in aSAH patients [110]. Two randomized controlled study suggested antifibrinolytic therapy might help to reduce the rebleeding risk, but this might promote vascular embolism events, especially long-term (more than 3 days) [111-112]. Three Cochrane reviews suggested that antifibrinolytic therapy can reduce the risk of rebleeding, it may increase the incidence of cerebral ischemic events [113-115]. Therefore, a short-term antifibrinolytic therapy might reduce the risk of rebleeding, but still requires high-level of evidence. For patients with intervention and surgical treatment, it is not recommended to use antifibrinolytic therapy for re-bleeding prevention purpose.

Recombinant activated factor VII might reduce the risk of rebleeding. Only one pilot study on dosage-escalation was conducted. Due to the unexpected number of serious adverse events (included 10 patients had cerebral infarction), the study was forced to abort [116]. Therefore, there is no evidence of recombinant activated factor VII used in SAH patients.

**Recommendations:**

1. **Antifibrinolytic drugs may help reduce the risk of rebleeding after SAH in short-term, but it is unable to improve the long-term clinical outcomes. If the patient still has a significant risk of rebleeding before intervention, and there is no absolute contraindication, tranexamic acid can be used for short-term (< 72h).**

**(Class IIb, Level of Evidence B). However, it should not be used in patients postsurgical or endovascular therapy (Class III, Level of Evidence C).**

## Section 3 Complications

### 1. Neurological complications

### 1.1 High intracranial pressure and hydrocephalus

SAH Patients with subarachnoid hemorrhage might likely to have high intracranial pressure. Several large-sample of retrospective studies found that elevated intracranial pressure might indicate poor prognosis [117-118]. A retrospective study in severe SAH patients showed that early and continuous infusion of hypertonic saline in patients with severe SAH reduced the frequency of intracranial pressure crises [119]. A meta-analysis confirmed this finding and suggested that it could reduce the intracranial pressure by 8.9mmHg on average [120]. Additionally, a meta-analysis showed Mannitol was effective in reducing pathological ICP, proportionally to the degree of intracranial hypertension [121].

For poor-graded patients, there was a high rate of intracranial pressure or hydrocephalus. Therefore, urgent surgical procedure such like hematoma removal might be helpful to improve the perioperative circumstances for aneurysm clipping or malformation resection [87].

Poor-graded SAH or young patient with massive effect is obvious combined with high intracranial pressure. Two RCTs and two meta-analysis of CSF

drainage confirmed the benefit of CSF drainage in SAH patients [122-125]. CSF drainage procedures by ventriculoperitoneal shunting or lumbar catheter were reported as useful and significantly reduce CVS and improve the clinical outcome [126-129]. A national meta-analysis indicated that the CSF drainage was associated the lower mortality and complication rate such as hydrocephalus and DCI [130]. The additional continuous tirofiban as a mono-antiplatelet therapy, neurapheresis or continuously nimodipine therapy might be promising [131-133].

Secondary hydrocephalus or cognitive impairment in patients with severe SAH is also common. Sudden increasing hydrocephalus might affect the cognitive function of poor-graded patient. It recommends Montreal Cognitive Scale (Montreal Cognitive Assessment, MOCA) and brief neuropsychological examination (Mini-Mental Status Examination, MMSE) as the primary screening assessment tools [134-135]. Since little was reported in SAH with cognitive impairment, it is not clear that there is a specific treatment for post-SAH cognitive impairment.

## Recommendations:

1. **Patients with clinical symptoms of increased intracranial pressure (ICP) can be treated with hypertonic saline or mannitol (Class IIa, Level of Evidence B).**
2. **For patients with elevated ICP or a massive effect, CSF drainage via ventriculostomy is recommended (Class I, Level of Evidence A). The additional use of IV tirofiban, and nimodipine therapy in patients with ventricular drainage or neurapheresis therapy might be helpful (Class IIb, Level of Evidence C).**

### 1.2 CVS and DCI

The International Multidisciplinary Research Group defined DCI after SAH and advocated for a separation of DCI from CVS after SAH [136]. Nevertheless, recent RCTs still mention CVS as the gold standard by catheter-guided DSA or as a composite endpoint along with clinic-radiologic ischemic findings. They use different criteria to define deterioration; delayed ischemic neurologic deficit (DIND); permanent neurologic deficits (PND); symptomatic, sonographic, or angiographic CVS; and delayed infarcts [136]. Recently, a novel method, continuous electroencephalography was proved that it could predict DCI after subarachnoid hemorrhage [137].

A number of large retrospective studies have shown that incidence of CVS was as high as 34%～45% [138-142], which was closely related to the incidence of DCI. Similar finding was reported in Chinese population, but the incidence of Han is significantly higher than other racial [140]. A post-hoc analysis of CONSCIOUS-1 trial confirmed this finding [142]. As was stated above, CSF drainage can reduce the incidence of CVS [123,128].

A large retrospective study found that higher hemoglobin levels at baseline might be a predictor of lower rates of DCI and better prognosis [143]. However, a small randomized controlled trial found that infusion of red blood cells did not reduce the incidence of cerebral infarction in patients at high risk of CVS

[144]. A large retrospective study also found that for late-onset DCI patient which suggested that infusing with red blood cells could not improve the prognosis of SAH patients [145].

There was no significant difference in the incidence and prognosis of CVS treated by surgeries or endovascular therapy [95,99,106,107]. The ischemic complications occur in about 6% of patients treated intraarterially for CVS[146].However, a recent observational study showed that endovascular treatment as a preventive strategy seemed to reduce the risk of DCI in patients with SAH and improve their functional outcome[147].Also, the evolution of balloon angioplasty was reported having a significant reduction of severe delayed CVS in patients with SAH[148].

Other agents with CVS prevention were listed in Supplemental Table 9.

**Recommendation1.Oral or IV nimodipine after SAH onset is recommended. (Class I, Level of Evidence A).**

**2. Statins have no additional benefit for delayed cerebral infarction or functional outcome and should not be used routinely in patients with aSAH (Class IIb, Level of Evidence B)**

3.F**asudil may be superior to nimodipine to prevent CVS. (Class IIa, Level of Evidence B).4. CSF drainage can significantly reduce the incidence of CVS and delayed cerebral infarction, and improve the overall treatment effect of patients with CVS (Class IIa, Level of Evidence B).5. Clazosentan might significantly reduce aSAH CVS-related morbidity/all-cause mortality in a dose-dependent manner;**

**however, no significant improvement on outcome. Considering it associated with complications such as anemia, pulmonary edema, low BP and other adverse reactions, it could be selectively used for patients with aSAH (Class IIa, Level of Evidence B).**

**6. Tirilazad could be added in SAH patients at a higher risk ofCVS (Class IIb, Level of Evidence B).**

**7. Agents such as cilostazol, IV edaravone, low molecular weight heparin, flunarizine, Ozagrel, Alprostadil might have the benefit of preventing delayed CVS (Class IIb, Level of Evidence B).**

**8. Intravenous magnesium sulphate does not improve clinical outcome after aSAH, therefore routine administration of magnesium might not be recommended (Class IIb, Level of Evidence A).**

**9. Higher hemoglobin levels at baseline indicates better outcome. However, packed red blood cell transfusion is not recommended (Class IIb, Level of Evidence B).**

**10. For SAH patients with severe cerebral vasospasm, endovascular treatment with balloon angioplasty may be considered (Class IIb, Level of Evidence B).**

## 1.3 Secondary epilepsy

The incidence of secondary epilepsy after SAH is 7% to 20%, and the incidence of early epilepsy is 2.3%~8.6%, the incidence of late epilepsy was 5.5% [149-151]. Risk factors such as severe CVS, hydrocephalus,

Admission with low GCS score, high Fisher score, surgical clipping of the aneurysm treatment, younger age, middle cerebral artery aneurysm were independent predictors of post-SAH epilepsy [149-151]. Patients with epilepsy occurrence was significantly worse than those who without [152,153]. A meta-analysis suggested that conventional prophylactic anti-epileptic drugs did not significantly reduce the incidence of secondary epilepsy, and the rate of CVS, DCI and poor prognosis are significantly increased [154]. A 14-year follow-up of randomized controlled study suggested that embolization therapy, compared to clipping, could significantly reduce incidence of seizures [150]. Another large cohort study found short-term levetiracetam showed non-superior of the incidence of epileptic seizures during hospitalization, compared to that of long-term phenytoin [155].

**Recommendations:**

1. **Routine prophylactic anti-epileptic drug use is not recommended. Such practice might increase the risk of CVS and DCI (Class III, Level of Evidence A).**
2. **For SAH patients with aneurysms located in the lateral fissure or having a convex SAH, there is a higher risk of seizure. If there is no contraindication, it is reasonable to treat with interventional embolization instead of surgical clipping. (Class IIa, Level of Evidence B).**
3. **For treating secondary epilepsy in SAH patients, long-term use of anti-epileptic drugs is recommended (Class IIa, Level of Evidence B).**

## 2.Non-neurological complications

### 2.1. Pneumonia

Pneumonia is one of the common complications in patients with severe SAH. The SAH related pneumonia ranged from 16%~ 67% [156-160], the incidence of pneumonia was similar in the Chinese population [159]. The incidence of pneumonia was correlated to the elder age, congestive heart failure, severity of SAH, and noninfectious complications [156]. Hypothermia, endothelial receptor antagonists and immunosuppressive therapy did not reduce the incident of pneumonia in several pilot studies [161-162]. A domestic study found that prophylactic antibiotics treatment may reduce the incidence of pneumonia [163]. A retrospective study found that pneumonia was a risk factor for poor prognosis of subarachnoid hemorrhage [164]. The early tracheostomy might reduce the incidence of pneumonia based a large-scaled nationwide study [165].

### Recommendation:

1. **SAH patients developed pneumonia have a poor prognosis and increased mortality (Class IIa , Level of evidence B ).**
2. **SAH patients who are older, developed status epilepticus, with severe SAH, and ventilator dependent have a higher risk of developing pneumonia (Class IIb , Level of evidence B ). If not contraindicated, prophylactic treatment with**

**antibiotics and early use of tracheostomy might be beneficial (Class IIb , Level of evidence C).**

## 2.2 DVT Prophylaxis

Deep venous thrombosis (DVT) is one of the serious complications after SAH. The incidence of deep vein thrombosis in patients with subarachnoid hemorrhage ranges from 0.1%~ 21%. [166-171]. The incidence of symptomatic deep vein thrombosis has been reported to range from 0.1%~1.2% in the Chinese population which is similar to foreign reports[170] . Most studies use conventional lower extremity B -ultrasound as a screening tool for ICU patients [168, 169]. Aneurysmal surgery, heparin-induced thrombocytopenia, male, ethnicity, aging, hypertension, high fibrinogen level, high Hunt-Hess score have been reported as risk factors of SAH [166-171]. Symptomatic deep vein thrombosis usually occurs within 2 weeks after the onset of SAH and 40% were reported within 5 to 9 days [168] . DVT is associated with the prolonged length of stay and poor outcome [168,171]. The effect of prophylactic subcutaneous heparin may be similar to intravenous injection of heparin [171]. A small randomized controlled study reported that fibrinolytic therapy is ineffective for DVT prevention[172] Another study reported aminocaproic acid may be safe in patients with SAH [173] .

## Recommendations

1. **Asymptomatic lower extremity DVT is not uncommon in patients with SAH and is associated with prolonged hospital stay and poor prognosis (Class IIa , Level of evidence A ).**

2. **The risk of DVT is relatively high in male patients post aneurysmal surgery who are bedridden and with severe SAH (Class IIa, Level of evidence B). Subcutaneous or intravenous heparin may be effective to prevent DVT if not contraindicated. (Class IIb, Level of evidence B).**

## 2.3 Other rare complications

Severe SAH may also cause some rare complications including hypotension, refractory hyponatremia, hypernatremia, hypoxemia, acute pulmonary edema and acute heart failure.

Hypotension is probably caused by vasospasm which occurs 5 to 7 days after onset of symptoms. Fluid resuscitation and nicardipine treatment may be effective[174]. 3H treatment with hypervolemia, hemodilution, hypertension is controversial. Recent studies suggest that hypervolemia treatment may cause DCI [175]. It may be indicated only in patients with hypovolemia with caution and central venous pressure should be carefully monitored during treatment [176,177] .

Refractory hyponatremia, syndrome of inappropriate antidiuretic hormone secretion (SIADH), cerebral salt wasting (CSW) and pulmonary edema may develop as a result of corticosteroid insufficiency, excessive fluid replacement and the use of diuretics. Sodium replacement could start in case of

hyponatremia with caution on the rate of infusion and close monitoring of central venous pressure if indicated [174, 178].

### Recommendations

1. **Routine 3H therapy is not recommended in patients with SAH. It may benefit some patients with hypovolemia. (Class III, Level of evidence B)**
2. **For patients with refractory hyponatremia, SIADH or CSW, sodium correction with restriction of fluids may be indicated and close monitoring of central venous pressure may be helpful (Class IIb, Level of evidence C).**

## Section 4 Prognosis and Recurrence

Aging, hypertension, hyperglycemia, hypernatremia are major predictors of poor outcome. Neurological complications like DCI and CVS, are associated with poor outcome. Patient with aSAH need to be initial endovascular treatment or urgent surgery as early as possible to prevent rebleeding.

# Supplemental Reference

[1]. DE ROOIJ N K, LINN F H, VAN DER PLAS J A, et al. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. J Neurol Neurosurg Psychiatry, 2007, 78(12): 1365-1372.

[2]. Guorong Liu, Yuechun Li, Guojuan Cheng, et al. Incidence of aneurysmal subarachnoid hemorrhage in Baotou, Inner Mongolia. Journal of Brain and Neurological Diseases (Chinese), 2016, 11: 670-674.

[3]. JIANG B, WANG W Z, CHEN H, et al. Incidence and trends of stroke and its subtypes in China: results from three large cities. Stroke, 2006, 37(1): 63-68.

[4]. LIANG W, HUANG R, LEE A H, et al. Hospitalizations for incident stroke in Shunde District, Foshan, South China. Neuroepidemiology, 2008, 30(2): 101-104.

[5]. Wei Zhang, Wei Su, Li He. Epidemiological Investigation on cerebral apoplexy in Community of Chendu City. West China Medical Journal(Chinese), 2011, 01: 41-43.

[6]. LIN HL, SOO K M, CHEN C W, et al. Incidence, national trend, and outcome of nontraumatic subarachnoid haemorrhage in Taiwan: initial lower mortality, poor long-term outcome. Biomed Res Int, 2014, 201:274572

[7]. KWON JW, LEE H J, HYUN M K, et al. Trends in the incidence of subarachnoid hemorrhage in South Korea from 2006-2009: an ecological

study. World Neurosurg, 2013, 79(3-4): 499-503.

[8]. BASSI P, BANDERA R, LOIERO M, et al. Warning signs in subarachnoid hemorrhage: a cooperative study. Acta Neurol Scand, 1991, 84(4): 277-281.

[9]. FONTANAROSA P B. Recognition of subarachnoid hemorrhage. Ann Emerg Med, 1989, 18(11): 1199-1205.

[10]. PERRY J J, STIELL I G, SIVILOTTI M L A, et al. Clinical Decision Rules to Rule Out Subarachnoid Hemorrhage for Acute Headache. Journal of the American Medical Association, 2013, 310(12): 1248-1255.

[11]. Ogunlaja OI, Cowan R. Subarachnoid Hemorrhage and Headache. Curr Pain Headache Rep. 2019 May 23;23(6):44

[12]. Glisic E K , Gardiner L , Josti L , et al. Inadequacy of Headache Management After Subarachnoid Hemorrhage. American Journal of Critical Care, 2016, 25(2):136-143.

[13]. PERRY J J, STIELL I G, SIVILOTTI M L A, et al. Sensitivity of computed tomography performed within six hours of onset of headache for diagnosis of subarachnoid haemorrhage: prospective cohort study. British Medical Journal, 2011, 343(

[14]. CORTNUM S, SORENSEN P, JORGENSEN J. Determining the sensitivity of computed tomography scanning in early detection of subarachnoid hemorrhage. Neurosurgery, 2010, 66(5): 900-902;

[15]. LAWTON M T, VATES G E. Subarachnoid Hemorrhage. N Engl J Med, 2017, 377(3): 257-266.

[16]. Morgenstern LB, Luna-Gonzales H, Huber JC Jr, et al. Worst headache and subarachnoid hemorrhage: prospective, modern computed tomography and spinal fluid analysis. Ann Emerg Med. 1998 Sep;32(3 Pt 1):297-304.

[17]. GROSS B A, FRERICHS K U, DU R. Sensitivity of CT angiography, T2-weighted MRI, and magnetic resonance angiography in detecting cerebral arteriovenous malformations and associated aneurysms. J Clin Neurosci, 2012, 19(8): 1093-1095.

[18]. KHURRAM A K T, LEYDEN J. Clinical associations and causes of convexity subarachnoid hemorrhage. Stroke, 2014, 45(4): 1151-1153.

[19]. Theodorou A, Lachanis S, Alexopoulos P Teaching NeuroImages: Acute convexity subarachnoid hemorrhage: An underrecognized presentation of CAA-ri.Neurology. 2019 Jul 30;

[20]. Calviere L, Viguier A, Patsoura S, Risk of Intracerebral Hemorrhage and Mortality After Convexity Subarachnoid Hemorrhage in Cerebral Amyloid Angiopathy.Stroke. 2019 Sep;50(9):2562-2564.

[21]. VIECO P T, SHUMAN W P, ALSOFROM G F, et al. Detection of circle of Willis aneurysms in patients with acute subarachnoid hemorrhage: a comparison of CT angiography and digital subtraction angiography. AJR Am J Roentgenol, 1995, 165(2): 425-430.

[22]. KOROGI Y, TAKAHASHI M, KATADA K, et al. Intracranial aneurysms: detection with three-dimensional CT angiography with volume rendering--

comparison with conventional angiographic and surgical findings. Radiology, 1999, 211(2): 497-506.

[23]. ALBERICO R A, PATEL M, CASEY S, et al. Evaluation of the circle of Willis with three-dimensional CT angiography in patients with suspected intracranial aneurysms. AJNR Am J Neuroradiol, 1995, 16(8): 1571-1578.

[24]. DONMEZ H, SERIFOV E, KAHRIMAN G, et al. Comparison of 16-row multislice CT angiography with conventional angiography for detection and evaluation of intracranial aneurysms. Eur J Radiol, 2011, 80(2): 455-461.

[25]. LUBICZ B, LEVIVIER M, FRANCOIS O, et al. Sixty-four-row multisection CT angiography for detection and evaluation of ruptured intracranial aneurysms: interobserver and intertechnique reproducibility. AJNR Am J Neuroradiol, 2007, 28(10): 1949-1955.

[26]. MCKINNEY A M, PALMER C S, TRUWIT C L, et al. Detection of aneurysms by 64-section multidetector CT angiography in patients acutely suspected of having an intracranial aneurysm and comparison with digital subtraction and 3D rotational angiography. AJNR Am J Neuroradiol, 2008, 29(3): 594-602.

[27]. LI Q, LV F, LI Y, et al. Evaluation of 64-section CT angiography for detection and treatment planning of intracranial aneurysms by using DSA and surgical findings. Radiology, 2009, 252(3): 808-815.

[28]. WESTERLAAN H E, VAN DIJK J M, JANSEN-VAN DER WEIDE M C, et al. Intracranial aneurysms in patients with subarachnoid hemorrhage: CT

angiography as a primary examination tool for diagnosis--systematic review and meta-analysis. Radiology, 2011, 258(1): 134-145.

[29]. WILLEMS P W, TAESHINEETANAKUL P, SCHENK B, et al. The use of 4D-CTA in the diagnostic work-up of brain arteriovenous malformations. Neuroradiology, 2012, 54(2): 123-131.

[30]. TURNER R C, LUCKE-WOLD B P, JOSIAH D, et al. Stereotactic radiosurgery planning based on time-resolved CTA for arteriovenous malformation: a case report and review of the literature. Acta Neurochir (Wien), 2016, 158(8): 1555-1562.

[31]. OGAWA S, LEE T M, KAY A R, et al. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci U S A, 1990, 87(24): 9868-9872.

[32]. OKANOVIC M, HILLIG B, BREUER F, et al. Time-of-flight MR-angiography with a helical trajectory and slice-super-resolution reconstruction. Magn Reson Med, 2018, 1-12

[33]. HAIFENG L, YONGSHENG X, YANGQIN X, et al. Diagnostic value of 3D time-of-flight magnetic resonance angiography for detecting intracranial aneurysm: a meta-analysis. Neuroradiology, 2017, 59(11): 1083-1092.

[34]. SAILER A M, WAGEMANS B A, NELEMANS P J, et al. Diagnosing intracranial aneurysms with MR angiography: systematic review and meta-analysis. Stroke, 2014, 45(1): 119-126.

[35]. VAN ROOIJ W J, SPRENGERS M E, DE GAST A N, et al. 3D rotational

angiography: the new gold standard in the detection of additional intracranial aneurysms. AJNR Am J Neuroradiol, 2008, 29(5): 976-979.

[36]. KOUSKOURAS C, CHARITANTI A, GIAVROGLOU C, et al. Intracranial aneurysms: evaluation using CTA and MRA. Correlation with DSA and intraoperative findings. Neuroradiology, 2004, 46(10): 842-850.

[37]. CHAPPELL E T, MOURE F C, GOOD M C. Comparison of computed tomographic angiography with digital subtraction angiography in the diagnosis of cerebral aneurysms: a meta-analysis. Neurosurgery, 2003, 52(3): 624-631.

[38]. FORSTER D M, STEINER L, HAKANSON S, et al. The value of repeat pan-angiography in cases of unexplained subarachnoid hemorrhage. J Neurosurg, 1978, 48(5): 712-716.

[39]. BAKKER N A, GROEN R J, FOUMANI M, et al. Repeat digital subtraction angiography after a negative baseline assessment in nonperimesencephalic subarachnoid hemorrhage: a pooled data meta-analysis. J Neurosurg, 2014, 120(1): 99-103.

[40]. Mohan M, Islim A, Dulhanty L, Parry-Jones A, Patel H.CT angiogram negative perimesencephalic subarachnoid hemorrhage: is a subsequent DSA necessary? A systematic review.J Neurointerv Surg. 2019 Jul 4. pii: neurintsurg-2019-015051.

[41]. HEIDENREICH J O, SCHILLING A M, UNTERHARNSCHEIDT F, et al. Assessment of 3D-TOF-MRA at 3.0 Tesla in the characterization of the

angioarchitecture of cerebral arteriovenous malformations: a preliminary study. Acta Radiol, 2007, 48(6): 678-686.

[42]. UNLU E, TEMIZOZ O, ALBAYRAM S, et al. Contrast-enhanced MR 3D angiography in the assessment of brain AVMs. Eur J Radiol, 2006, 60(3): 367-378.

[43]. GRIFFITHS P D, HOGGARD N, WARREN D J, et al. Brain arteriovenous malformations: assessment with dynamic MR digital subtraction angiography. AJNR Am J Neuroradiol, 2000, 21(10): 1892-1899.

[44]. KRINGS T, HANS F. New developments in MRA: time-resolved MRA. Neuroradiology, 2004, 46 Suppl 2:s214-222.

[45]. MIYASAKA T, TAOKA T, NAKAGAWA H, et al. Application of susceptibility weighted imaging (SWI) for evaluation of draining veins of arteriovenous malformation: utility of magnitude images. Neuroradiology, 2012, 54(11): 1221-1227.

[46]. TRANVINH E, HEIT J J, HACEIN-BEY L, et al. Contemporary Imaging of Cerebral Arteriovenous Malformations. AJR Am J Roentgenol, 2017, 208(6): 1320-1330.

[47]. CHANG R F D. Isolated cortical venous thrombosis presenting as subarachnoid hemorrhage: a report of three cases. Am J Neuroradiol, 2004, 25(10): 1676-1679.

[48]. OSHIRO E M, WALTER K A, PIANTADOSI S, et al. A new subarachnoid hemorrhage grading system based on the Glasgow Coma Scale: a

comparison with the Hunt and Hess and World Federation of Neurological Surgeons Scales in a clinical series. Neurosurgery, 1997, 41(1): 140-147.

[49]. LINDVALL P, RUNNERSTAM M, BIRGANDER R, et al. The Fisher grading correlated to outcome in patients with subarachnoid haemorrhage. Br J Neurosurg, 2009, 23(2): 188-192.

[50]. FRONTERA J A, CLAASSEN J, SCHMIDT J M, et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. Neurosurgery, 2006, 59(1): 21-27.

[51]. DUPONT S A, WIJDICKS E F, MANNO E M, et al. Prediction of angiographic vasospasm after aneurysmal subarachnoid hemorrhage: value of the Hijdra sum scoring system. Neurocrit Care, 2009, 11(2): 172-176.

[52]. WOERTGEN C, ULLRICH O W, ROTHOERL R D, et al. Comparison of the Claassen and Fisher CT classification scale to predict ischemia after aneurysmatic SAH? Zentralbl Neurochir, 2003, 64(3): 104-108.

[53]. DEGEN L A, DORHOUT MEES S M, ALGRA A, et al. Interobserver variability of grading scales for aneurysmal subarachnoid hemorrhage. Stroke, 2011, 42(6): 1546-1549.

[54]. DENGLER N F, DIESING D, SARRAFZADEH A, et al. The Barrow Neurological Institute Scale Revisited: Predictive Capabilities for Cerebral Infarction and Clinical Outcome in Patients with Aneurysmal Subarachnoid Hemorrhage. Neurosurgery, 2017, 81(2): 341-349.

[55]. FRONTERA J A, CLAASSEN J, SCHMIDT J M, et al. Prediction of

symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. Neurosurgery, 2006, 59(1): 21-27.

[56]. RUSH B, ROMANO K, ASHKANANI M, et al. Impact of hospital case-volume on subarachnoid hemorrhage outcomes: A nationwide analysis adjusting for hemorrhage severity. J Crit Care, 2017, 37:240-243.

[57]. PANDEY A S, GEMMETE J J, WILSON T J, et al. High Subarachnoid Hemorrhage Patient Volume Associated With Lower Mortality and Better Outcomes. Neurosurgery, 2015, 77(3): 462-470.

[58]. LEE S H, SONG K J. The Relationship between Clinical Outcome in Subarachnoidal Hemorrhage Patients with Emergency Medical Service Usage and Interhospital Transfer. 2015, 30(12): 1889-1895.

[59]. Dijkland SA, Jaja BNR, van der Jagt M et al. Between-center and between-country differences in outcome after aneurysmal subarachnoid hemorrhage in the Subarachnoid Hemorrhage International Trialists (SAHIT) repository. J Neurosurg. 2019 Aug 23:1-9.

[60]. NUNO M, PATIL C G, LYDEN P, et al. The effect of transfer and hospital volume in subarachnoid hemorrhage patients. Neurocrit Care, 2012, 17(3): 312-323.

[61]. BERMAN M F, SOLOMON R A, MAYER S A, et al. Impact of hospital-related factors on outcome after treatment of cerebral aneurysms. Stroke, 2003, 34(9): 2200-2207.

[62]. CROSS D T, 3RD, TIRSCHWELL D L, CLARK M A, et al. Mortality rates

after subarachnoid hemorrhage: variations according to hospital case volume in 18 states. J Neurosurg, 2003, 99(5): 810-817.

[63]. BARDACH N S, ZHAO S, GRESS D R, et al. Association between subarachnoid hemorrhage outcomes and number of cases treated at California hospitals. Stroke, 2002, 33(7): 1851-1856.

[64]. Boogaarts HD, van Amerongen MJ, de Vries J, Westert GP, Verbeek AL, Grotenhuis JA, et al. Caseload as a factor for outcome in aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. J Neurosurg.2014 Mar;120(3):605-11.

[65]. JOSEPHSON S A, DOUGLAS V C, LAWTON M T, et al. Improvement in intensive care unit outcomes in patients with subarachnoid hemorrhage after initiation of neurointensivist co-management. J Neurosurg, 2010, 112(3): 626-630.

[66]. GUO L M, ZHOU H Y, XU J W, et al. Risk factors related to aneurysmal rebleeding [J]. World Neurosurg, 2011, 76(3-4): 292-8

[67]. OHKUMA H, TSURUTANI H, SUZUKI S. Incidence and significance of early aneurysmal rebleeding before neurosurgical or neurological management [J]. Stroke, 2001, 32(5): 1176-80.

[68]. VLAK M H, RINKEL G J, GREEBE P, et al. Trigger factors and their attributable risk for rupture of intracranial aneurysms: a case-crossover study [J]. Stroke, 2011, 42(7): 1878-82.

[69]. LIN Q S, PING C, LIN Y X, et al. Systolic Blood Pressure Variability is a

Novel Risk Factor for Rebleeding in Acute Subarachnoid Hemorrhage: A Case-Control Study [J]. Medicine (Baltimore), 2016, 95(11): e3028.

[70]. Riis J, Nordestgaard BG, Jensen GB, Afzal S.Secular trends in risk of stroke according to body mass index and blood pressure, 1976-2017. Neurology. 2019 Aug 30]

[71]. Mutoh T, Kazumata K, Terasaka S, Taki Y, Suzuki A, Ishikawa T. Early intensive versus minimally invasive approach to postoperative hemodynamic management after subarachnoid hemorrhage Stroke. 2014 May;45(5):1280-4.

[72]. Togashi K, Joffe AM, Sekhar L, et al. Randomized pilot trial of intensive management of blood pressure or volume expansion in subarachnoid hemorrhage (IMPROVES). Neurosurgery. 2015 Feb;76(2):125-34

[73]. Pickard JD, Murray GD, Illingworth R. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. BMJ. 1989 Mar 11;298(6674):636-42.

[74]. WOLOSZYN A V, MCALLEN K J, FIGUEROA B E, et al. Retrospective evaluation of nicardipine versus labetalol for blood pressure control in aneurysmal subarachnoid hemorrhage. Neurocrit Care, 2012, 16(3): 376-380.

[75]. Chen G, Arima H, Wu G, Heeley E, Delcourt C, Zhang P,et al. Subarachnoid extension of intracerebral hemorrhage and 90-day outcomes in INTERACT2. Stroke. 2014 Jan;45(1):258-60

[76]. Kieninger M, Gruber M, Knott I, Dettmer K, Oefner PJ, Bele S, et al. Incidence of Arterial Hypotension in Patients Receiving Peroral or Continuous Intra-arterial Nimodipine After Aneurysmal or Perimesencephalic Subarachnoid Hemorrhage.Neurocrit Care. 2019 Aug;31(1):32-39.

[77]. MATSUDA M, WATANABE K, SAITO A, et al. Circumstances, activities, and events precipitating aneurysmal subarachnoid hemorrhage. J Stroke Cerebrovasc Dis, 2007, 16(1): 25-29.

[78]. KRUYT N D, BIESSELS G J, DE HAAN R J, et al. Hyperglycemia and clinical outcome in aneurysmal subarachnoid hemorrhage: a meta-analysis. Stroke, 2009, 40(6): e424-430.

[79]. KRUYT N D, ROOS Y W, DORHOUT MEES S M, et al. High mean fasting glucose levels independently predict poor outcome and delayed cerebral ischaemia after aneurysmal subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry, 2008, 79(12): 1382-1385.

[80]. DUMONT T, RUGHANI A, SILVER J, et al. Diabetes mellitus increases risk of vasospasm following aneurysmal subarachnoid hemorrhage independent of glycemic control. Neurocrit Care, 2009, 11(2): 183-189.

[81]. THIELE R H, POURATIAN N, ZUO Z, et al. Strict glucose control does not affect mortality after aneurysmal subarachnoid hemorrhage. Anesthesiology, 2009, 110(3): 603-610

[82]. Ogunlaja OI, Cowan R. Subarachnoid Hemorrhage and Headache.Curr

Pain Headache Rep. 2019 May 23;23(6):44

[83]. Long D, Koyfman A, Long B. The Thunderclap Headache: Approach and Management in the Emergency Department. J Emerg Med. 2019 Jun;56(6):633-641.

[84]. Graffeo CS, Perry A, Wijdicks EF. Subarachnoid Hemorrhage and Spinal Subdural Hematoma Due to Acute CSF Hypotension. Neurocrit Care. 2017 Feb;26(1):109-114

[85]. SPETZLER R F, MCDOUGALL C G, ZABRAMSKI J M, et al. The Barrow Ruptured Aneurysm Trial: 6-year results. J Neurosurg, 2015, 123(3): 609-617.

[86]. MINAKAWA T, KOIKE T, FUJII Y, et al. Long term results of ruptured aneurysms treated by coating. Neurosurgery, 1987, 21(5): 660-663.

[87]. VAN LOON J, WILMS G, VAN CALENBERGH F, et al. Poor-grade aneurysmal subarachnoid hemorrhage: outcome after treatment with urgent surgery. Neurosurgery, 2004, 55(1): 264-265; author reply 265-266.

[88]. XU F, XU B, HUANG L, et al. Surgical Treatment of Large or Giant Fusiform Middle Cerebral Artery Aneurysms: A Case Series. World Neurosurg, 2018, 115:e252-e262

[89]. SHARMA B S, GUPTA A, AHMAD F U, et al. Surgical management of giant intracranial aneurysms. Clin Neurol Neurosurg, 2008, 110(7): 674-681.

[90]. BARROW D L, CAWLEY C M. Surgical management of complex

intracranial aneurysms. Neurol India, 2004, 52(2): 156-162.

[91]. CHOUDHRI O, MUKERJI N, STEINBERG G K. Combined endovascular and microsurgical management of complex cerebral aneurysms. Front Neurol, 2013, 4:108.

[92]. HACEIN-BEY L, CONNOLLY E S, JR., MAYER S A, et al. Complex intracranial aneurysms: combined operative and endovascular approaches. Neurosurgery, 1998, 43(6): 1304-131.

[93]. SCHAAFSMA J D, SPRENGERS M E, VAN ROOIJ W J, et al. Long-term recurrent subarachnoid hemorrhage after adequate coiling versus clipping of ruptured intracranial aneurysms. Stroke, 2009, 40(5): 1758-1763.

[94]. RAPER D M, ALLAN R. International subarachnoid trial in the long run: critical evaluation of the long-term follow-up data from the ISAT trial of clipping vs coiling for ruptured intracranial aneurysms. Neurosurgery, 2010, 66(6): 1166-1169.

[95]. Wang HY, Song J, Gao F, Duan XD, Gao X, Wang Y, Cheng HB, Nan CR, Zhao D. Outcomes of microsurgical clipping vs coil embolization for ruptured aneurysmal subarachnoid hemorrhage: A multicenter real-world analysis of 583 patients in China. Medicine (Baltimore). 2019 Aug;98(33):e16821.

[96]. SHIRAO S, YONEDA H, KUNITSUGU I, et al. Preoperative prediction of outcome in 283 poor-grade patients with subarachnoid hemorrhage: a project of the Chugoku-Shikoku Division of the Japan Neurosurgical Society

[J]. Cerebrovasc Dis, 2010, 30(2): 105-13.

[97]. Akinduro OO, Vivas-Buitrago TG, Haranhalli N, Predictors of Ventriculoperitoneal shunting following Subarachnoid Hemorrhage treated with External Ventricular Drainage.Neurocrit Care. 2019 Aug 13.

[98]. VELTHUIS B K, RINKEL G J, RAMOS L M, et al. Subarachnoid hemorrhage: aneurysm detection and preoperative evaluation with CT angiography. Radiology, 1998, 208(2): 423-430.

[99]. MOLYNEUX A, KERR R, STRATTON I, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. Lancet, 2002, 360(9342): 1267-1274.

[100]. MACHI P, COSTALAT V, LOBOTESIS K, et al. LEO Baby Stent Use following Balloon-Assisted Coiling: Single- and Dual-Stent Technique--Immediate and Midterm Results of 29 Consecutive Patients. AJNR Am J Neuroradiol, 2015, 36(11): 2096-2103.

[101]. AMENTA P S, DALYAI R T, KUNG D, et al. Stent-assisted coiling of wide-necked aneurysms in the setting of acute subarachnoid hemorrhage: experience in 65 patients. Neurosurgery, 2012, 70(6): 1415-1429.

[102]. LIN N, BROUILLARD A M, KRISHNA C, et al. Use of Coils in Conjunction with the Pipeline Embolization Device for Treatment of Intracranial Aneurysms. Neurosurgery, 2015, 76(2): 142-149.

[103]. AIYAGARI V, CROSS D T, 3RD, DEIBERT E, et al. Safety of hemodynamic

augmentation in patients treated with Guglielmi detachable coils after acute aneurysmal subarachnoid hemorrhage. Stroke, 2001, 32(9): 1994-1997.

[104]. Wakhloo A K,Lylyk P,de Vries J et al. Surpass flow diverter in the treatment of intracranial aneurysms: a prospective multicenter study.[J] .AJNR Am J Neuroradiol, 2015, 36: 98-107.

[105]. Raymond Jean,Gentric Jean-Christophe,Darsaut Tim E et al. Flow diversion in the treatment of aneurysms: a randomized care trial and registry.[J] .J. Neurosurg., 2017, 127: 454-462..

[106]. ELIJOVICH L, HIGASHIDA R T, LAWTON M T, et al. Predictors and outcomes of intraprocedural rupture in patients treated for ruptured intracranial aneurysms: the CARAT study. Stroke, 2008, 39(5): 1501-1506.

[107]. Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M, Yarnold JA, et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomized comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. Lancet. 2005;366(9488):809-17.

[108]. Turjman Francis,Levrier Olivier,Combaz Xavier et al. EVIDENCE trial: design of a phase 2, randomized, controlled, multicenter study comparing flow diversion and traditional endovascular strategy in unruptured saccular wide-necked intracranial aneurysms.[J] .Neuroradiology, 2015, 57: 49-54.

[109]. Turk A S,Martin R H,Fiorella D et al. Flow diversion versus traditional

endovascular coiling therapy: design of the prospective LARGE aneurysm randomized trial.[J] .AJNR Am J Neuroradiol, 2014, 35: 1341-5.

[110]. HILLMAN J, FRIDRIKSSON S, NILSSON O, et al. Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurysmal subarachnoid hemorrhage: a prospective randomized study. J Neurosurg, 2002, 97(4): 771-778.

[111]. VERMEULEN M, LINDSAY K W, MURRAY G D, et al. Antifibrinolytic treatment in subarachnoid hemorrhage. N Engl J Med, 1984, 311(7): 432-437.

[112]. ROOS Y. Antifibrinolytic treatment in subarachnoid hemorrhage: a randomized placebo-controlled trial. STAR Study Group. Neurology, 2000, 54(1): 77-82.

[113]. ROOS Y, RINKEL G, VERMEULEN M, et al. Antifibrinolytic therapy for aneurysmal subarachnoid hemorrhage: a major update of a cochrane review. Stroke, 2003, 34(9): 2308-2309.

[114]. ROOS Y B, RINKEL G J, VERMEULEN M, et al. Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev, 2003, 2: CD001245.

[115]. BAHAROGLU M I, GERMANS M R, RINKEL G J, et al. Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage. Cochrane Database Syst Rev, 2013, 8: CD001245.

[116]. PICKARD J D, KIRKPATRICK P J, MELSEN T, et al. Potential role of

NovoSeven in the prevention of rebleeding following aneurysmal subarachnoid haemorrhage. Blood Coagul Fibrinolysis, 2000, 11 Suppl 1:S117-120.

[117]. RYTTLEFORS M, HOWELLS T, NILSSON P, et al. Secondary insults in subarachnoid hemorrhage: occurrence and impact on outcome and clinical deterioration. Neurosurgery, 2007, 61(4): 704-714.

[118]. HEUER G G, SMITH M J, ELLIOTT J P, et al. Relationship between intracranial pressure and other clinical variables in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg, 2004, 101(3): 408-416.

[119]. HAUER EM, STARK D, STAYKOV D, et al. Early continuous hypertonic saline infusion in patients with severe cerebrovascular disease. Crit Care Med, 2011, 39(7): 1766-1772.

[120]. PASARIKOVSKI C R, ALOTAIBI N M, AL-MUFTI F, et al. Hypertonic Saline for Increased Intracranial Pressure After Aneurysmal Subarachnoid Hemorrhage: A Systematic Review. World Neurosurg, 2017, 105:1-6.

[121]. Poole D, Citerio G, Helbok R, Ichai C, Meyfroidt G,et al. Evidence for Mannitol as an Effective Agent Against Intracranial Hypertension: An Individual Patient Data Meta-analysis.Neurocrit Care. 2019 Jul 1.

[122]. Al-Tamimi YZ, Bhargava D, Feltbower RG, Hall G, Goddard AJ, Quinn AC, et al. Lumbar drainage of cerebrospinal fluid after aneurysmal subarachnoid hemorrhage: a prospective, randomized, controlled trial (LUMAS).Stroke. 2012; 43:677–682

[123]. Borkar SA, Singh M, Kale SS, Suri A, Chandra PS, Kumar R, et al. Spinal cerebrospinal fluid drainage for prevention of vasospasm in aneurysmal subarachnoid hemorrhage: a prospective, randomized controlled study.Asian J Neurosurg. 2018; 13:238–246. doi: 10.4103/1793-5482.228512

[124]. Alcalá-Cerra G, Paternina-Caicedo Á, Díaz-Becerra C, Moscote-Salazar LR, Gutiérrez-Paternina JJ, Niño-Hernández LM; En representación del Grupo de Investigación en Ciencias de la Salud y Neurociencias (CISNEURO). External lumbar cerebrospinal fluid drainage in patients with aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis of controlled trials.Neurologia. 2016; 31:431–444.

[125]. Qian C, Yu X, Chen J, Gu C, Wang L, Chen G, et al. Effect of the drainage of cerebrospinal fluid in patients with aneurismal subarachnoid hemorrhage: A meta-analysis. Medicine (Baltimore). 2016; 95:e5140

[126]. Akinduro OO, Vivas-Buitrago TG, Haranhalli N, Predictors of Ventriculoperitoneal shunting following Subarachnoid Hemorrhage treated with External Ventricular Drainage.Neurocrit Care. 2019 Aug 13.

[127]. Roelz R, Coenen VA, Scheiwe C, Niesen WD, Egger K, Csok I, et al. Stereotactic catheter ventriculocisternostomy for clearance of subarachnoid hemorrhage: a matched cohort study.Stroke. 2017; 48:2704–2709. doi: 10.1161/STROKEAHA.117.018397

[128]. Klimo P, Kestle JR, MacDonald JD, Schmidt RH. Marked reduction of

cerebral vasospasm with lumbar drainage of cerebrospinal fluid after subarachnoid hemorrhage.J Neurosurg. 2004; 100:215–224. doi: 10.3171/jns.2004.100.2.0215

[129]. Ohshima T, Isaji T, Miyachi S, Matsuo N, Kawaguchi R, Maejima R, Takayasu M. Efficacy of three-dimensional rotational fluoroscopic unit guidance for lumbar cerebrospinal fluid drainage among patients with unsuccessful initial attempt at bedside.Interv Neuroradiol. 2019 Jun;25(3):357-360

[130]. Weizheng Li, Ming Liu, Shejun Feng, Bo Wu, Wei Dong. Lumbar Continuous Drainage of the Cerebrospinal Fluid Therapy for Subarachnoid Hemorrhage: A Systematic Review. Chinese Journal of Evidence-Based Medicine(Chinese). 2009, 2: 207-212.

[131]. Limaye K, Zanaty M, Hudson J, Nakagawa D, Al Kasab S, Alvarez C, Dandapat S, Kung DK, Ortega-Gutierrez S, Jabbour P, Samaniego EA, Hasan D. The Safety and Efficacy of Continuous Tirofiban as a Monoantiplatelet Therapy in the Management of Ruptured Aneurysms Treated Using Stent-Assisted Coiling or Flow Diversion and Requiring Ventricular Drainage.Neurosurgery. 2019 Jul 12.

[132]. Blackburn SL, Grande AW, Swisher CB, Hauck EF, Jagadeesan B, Provencio JJ. Prospective Trial of Cerebrospinal Fluid Filtration After Aneurysmal Subarachnoid Hemorrhage via lumbar catheter (PILLAR). Stroke. 2019 Sep;50(9):2558-2561

[133]. Hänggi D, Etminan N, Aldrich F, Steiger HJ, Mayer SA, Diringer MN, et al. Randomized, open-label, phase 1/2a study to determine the maximum tolerated dose of intraventricular sustained release nimodipine for subarachnoid hemorrhage (NEWTON [Nimodipine Microparticles to Enhance Recovery While Reducing Toxicity After Subarachnoid Hemorrhage]). Stroke. 2017;48:145–51.

[134]. ZAKI GHALI MG S V, WAGNER K, RAO C, CHEN SR, JOHNSON JN, KAN P. Cognitive Sequelae of Unruptured and Ruptured Intracranial Aneurysms and their Treatment: Modalities for Neuropsychological Assessment. World Neurosurg, 2018, 120:537-549.

[135]. Huenges Wajer IMC, Hendriks ME,et al. The relationship between ischaemic brain lesions and cognitive outcome after aneurysmal subarachnoid haemorrhage. J Neurol. 201;266(9):2252-2257.

[136]. Gregory Kapinos. Redefining Secondary Injury After Subarachnoid Hemorrhage in Light of Multimodal Advanced Neuroimaging, Intracranial and Transcranial Neuromonitoring: Beyond Vasospasm. Acta Neurochirurgica. 2014, 120:259-267

[137]. ROSENTHAL E S, BISWAL S, ZAFAR S F, et al. Continuous electroencephalography predicts delayed cerebral ischemia after subarachnoid hemorrhage: A prospective study of diagnostic accuracy [J]. Annals of neurology, 2018, 83(5): 958-69.

[138]. BROWN R J, KUMAR A, DHAR R, et al. The relationship between delayed

infarcts and angiographic vasospasm after aneurysmal subarachnoid hemorrhage. Neurosurgery, 2013, 72(5): 702-707.

[139]. AYLING O G, IBRAHIM G M, ALOTAIBI N M, et al. Dissociation of Early and Delayed Cerebral Infarction After Aneurysmal Subarachnoid Hemorrhage. Stroke, 2016, 47(12): 2945-2951.

[140]. MIJITI M, MIJITI P, AXIER A, et al. Incidence and Predictors of Angiographic Vasospasm, Symptomatic Vasospasm and Cerebral Infarction in Chinese Patients with Aneurysmal Subarachnoid Hemorrhage. PLoS One, 2016, 11(12): e0168657.

[141]. VERGOUWEN M D, ILODIGWE D, MACDONALD R L. Cerebral infarction after subarachnoid hemorrhage contributes to poor outcome by vasospasm-dependent and -independent effects. Stroke, 2011, 42(4): 924-929.

[142]. Crowley RW, Medel R, Dumont AS, et al. Angiographic vasospasm is strongly correlated with cerebral infarction after subarachnoid hemorrhage.Stroke. 2011 Apr;42(4):919-23.

[143]. NAIDECH A M, DRESCHER J, AULT M L, et al. Higher hemoglobin is associated with less cerebral infarction, poor outcome, and death after subarachnoid hemorrhage. Neurosurgery, 2006, 59(4): 775-779.

[144]. NAIDECH A M, SHAIBANI A, GARG R K, et al. Prospective, randomized trial of higher goal hemoglobin after subarachnoid hemorrhage. Neurocrit Care, 2010, 13(3): 313-320.

[145]. KUMAR M A, LEVINE J, FAERBER J, et al. The Effects of Red Blood Cell Transfusion on Functional Outcome after Aneurysmal Subarachnoid Hemorrhage. World Neurosurg, 2017, 108:807-816.

[146]. Adami D, Berkefeld J, Platz J, et al. Complication rate of intraarterial treatment of severe cerebral vasospasm after subarachnoid hemorrhage with nimodipine and percutaneous transluminal balloon angioplasty: Worth the risk? J Neuroradiol. 2019 Feb;46(1):15-24.

[147]. Jabbarli R, Pierscianek D, Rölz R, et al. Endovascular treatment of cerebral vasospasm after subarachnoid hemorrhage: More is more.Neurology. 2019 Jul 30;93(5):e458-e466

[148]. JESTAEDT L, PHAM M, BARTSCH A, et al. The impact of balloon angioplasty on the evolution of vasospasm-related infarction after aneurysmal subarachnoid hemorrhage [J/OL] 2008, 62(3):610-7

[149]. CLAASSEN J, PEERY S, KREITER K T, et al. Predictors and clinical impact of epilepsy after subarachnoid hemorrhage. Neurology, 2003, 60(2): 208-214.

[150]. HART Y, SNEADE M, BIRKS J, et al. Epilepsy after subarachnoid hemorrhage: the frequency of seizures after clip occlusion or coil embolization of a ruptured cerebral aneurysm: results from the International Subarachnoid Aneurysm Trial. J Neurosurg, 2011, 115(6): 1159-1168.

[151]. RAPER D M, STARKE R M, KOMOTAR R J, et al. Seizures after

aneurysmal subarachnoid hemorrhage: a systematic review of outcomes. World Neurosurg, 2013, 79(5-6): 682-690.

[152]. ROSENGART A, HUO J, TOLENTINO J, et al. Outcome in patients with subarachnoid hemorrhage treated with antiepileptic drugs [J/OL] 2007, 107(2):253-260

[153]. Hui Wang, Xinjie Ning, Juncheng Luo, Chuan Chen, Xinhua Lu. Risk factor analysis of seizures after aneurysmal subarachnoid hemorrhage. Chinese Journal of Neurosurgery(Chinese).32(3): 274-278

[154]. Dmytriw AA, Maragkos GA, Zuccato J, et al. Use of Antiepileptic Drugs in Aneurysmal Subarachnoid Hemorrhage.Can J Neurol Sci. 2019 Jul;46(4):423-429

[155]. MURPHY-HUMAN T, WELCH E, ZIPFEL G, et al. Comparison of short-duration levetiracetam with extended-course phenytoin for seizure prophylaxis after subarachnoid hemorrhage. World Neurosurg, 2011, 75(2): 269-274

[156]. CINOTTI R, DORDONNAT-MOYNARD A, FEUILLET F, et al. Risk factors and pathogens involved in early ventilator-acquired pneumonia in patients with severe subarachnoid hemorrhage. Eur J Clin Microbiol Infect Dis, 2014, 33(5): 823-830.

[157]. RADOLF S, SMOLL N, DRENCKHAHN C, et al. Cerebral lactate correlates with early onset pneumonia after aneurysmal SAH. Transl Stroke Res, 2014, 5(2): 278-285.

[158]. DASENBROCK H H, RUDY R F, SMITH T R, et al. Hospital-Acquired Infections after Aneurysmal Subarachnoid Hemorrhage: A Nationwide Analysis. World Neurosurg, 2016, 88：459-474.

[159]. HONGYU WANG, XIANG XU, YUMEI MA, JIANZHONG CUI, KAIJIE WANG, JUN HONG. Pathogenic bacteria causing pulmonary infection in elderly patients with subarachnoid hemorrhage and treatment programs. Chinese Journal of Nosocomiology(Chinese).2013, 15: 3619-3623.

[160]. LI LUYING R, YOU C, CHAUDHARY B. Intraoperative mild hypothermia for postoperative neurological deficits in people with intracranial aneurysm [J/OL] 2016, 3): http://onlinelibrary.wiley.com/store/10.1002/14651858.CD008445.pub3/asset/CD008445.pdf?v=1&t=jdrmmgvp&s=5143ca27f57a2918cb14dcbb6f1b37cabc54a939

[161]. SARRAFZADEH A, SCHLENK F, MEISEL A, et al. Immunodepression after aneurysmal subarachnoid hemorrhage. Stroke, 2011, 42(1): 53-58.

[162]. GUO J, SHI Z, YANG K, et al. Endothelin receptor antagonists for subarachnoid hemorrhage. Cochrane Database Syst Rev, 2012, 9: Cd008354.

[163]. Xinli Li, Qiang Xia, Quncai Liu, Prevention and treatment for Post subarachnoid hemorrhage pneumonia. Journal of Practical Medicine Pharmacy, 2002, 06: 423.

[164]. Sun Shiji, Yong Ying. Mortality analysis of 150 cases of subarachnoid

hemorrhage. Stroke and Neurological disease(Chinese). 1986, 01: 14-15.

[165]. Dasenbrock HH, Rudy RF, Gormley WB, Frerichs KU, Aziz-Sultan MA, Du R. The Timing of Tracheostomy and Outcomes After Aneurysmal Subarachnoid Hemorrhage: A Nationwide Inpatient Sample Analysis. Neurocrit Care. 2018 Dec;29(3):326-335.

[166]. SERRONE J C, WASH E M, HARTINGS J A, et al. Venous thromboembolism in subarachnoid hemorrhage. World Neurosurg, 2013, 80(6): 859-863.

[167]. KSHETTRY V R, ROSENBAUM B P, SEICEAN A, et al. Incidence and risk factors associated with in-hospital venous thromboembolism after aneurysmal subarachnoid hemorrhage. J Clin Neurosci, 2014, 21(2): 282-286.

[168]. LIANG C W, SU K, LIU J J, et al. Timing of deep vein thrombosis formation after aneurysmal subarachnoid hemorrhage. J Neurosurg, 2015, 123(4): 891-896.

[169]. HENWOOD P C, KENNEDY T M, THOMSON L, et al. The incidence of deep vein thrombosis detected by routine surveillance ultrasound in neurosurgery patients receiving dual modality prophylaxis. J Thromb Thrombolysis, 2011, 32(2): 209-214.

[170]. Wei Li, Aiping Yan, Wenbin Li, Dejun Zhu. Risk factors of deep veins thrombosis in the lower limbs of patients with subarachnoid hemorrhage and prevention strategies. Journal of International Neurology and

Neurosurgery(Chiese). 2012, 06: 504-506.

[171]. SIMARD J M, ALDRICH E F, SCHREIBMAN D, et al. Low-dose intravenous heparin infusion in patients with aneurysmal subarachnoid hemorrhage: a preliminary assessment. J Neurosurg, 2013, 119(6): 1611-1619.

[172]. BAHAROGLU MERIH I, GERMANS MENNO R, RINKEL GABRIEL J E, et al. Antifibrinolytic therapy for aneurysmal subarachnoid haemorrhage [J/OL] 2013, 8): http://onlinelibrary.wiley.com/store/10.1002/14651858.CD001245.pub2/asset/CD001245.pdf?v=1&t=jes1y7jq&s=87ea126e649e003abeb5c9773822049d723c63c7.

[173]. HUI F K, SCHUETTE A J, LIEBER M, et al. epsilon-Aminocaproic acid in angiographically negative subarachnoid hemorrhage patients is safe: a retrospective review of 83 consecutive patients. Neurosurgery, 2012, 70(3): 702-705.

[174]. HALL A et al. The Extracranial Consequences of Subarachnoid Hemorrhage. World Neurosurg, 2018, 109:381-392.

[175]. VERGOUW LJM E M, BERGMANS B, DIPPEL DWJ, LINGSMA HF, VERGOUWEN MDI, WILLEMS PWA, OLDENBEUVING AW, BAKKER J, VAN DER JAGT M. High Early Fluid Input After Aneurysmal Subarachnoid Hemorrhage: Combined Report of Association with Delayed Cerebral Ischemia and Feasibility of Cardiac Output-Guided Fluid Restriction. J

Intensive Care Med, 2017, 1:1-9

[176]. [ENGQUIST H R E, RONNE-ENGSTR M E, NILSSON P, LEW N A, ENBLAD P. Effect of HHH-Therapy on Regional CBF after Severe Subarachnoid Hemorrhage Studied by Bedside Xenon-Enhanced CT. Neurocrit Care, 2018, 28(2): 143-151.

[177]. DIRINGER MN Z A. Aneurysmal Subarachnoid Hemorrhage: Strategies for Preventing Vasospasm in the Intensive Care Unit. Semin Respir Crit Care Med, 2017, 38(6): 760-767.

[178]. MURTHY SB S S, RAO CP, BERSHAD EM, SUAREZ JI. Neurogenic Stunned Myocardium Following Acute Subarachnoid Hemorrhage: Pathophysiology and Practical Considerations. J Intensive Care Med 2015, 30(6): 318-325.

[179]. Guangjian Liu, Zhengjun Wang, Yunpu WANG , et al.. Efficacy and safety of prophylactic use of nimodipine in patients with aneurysmal subarachnoid hemorrhage: a meta-analysis. Chinese Journal of Cerebrovascular Diseases (Chinese). 2011, 1: 28-33,46.

[180]. Wen He. Different dosages of nimodipine to prevent cerebral vascular spasms after subarachnoid hemorrhage. Journal of Clinical Neurology (Chinese). 2005, 18(2): 149-150

[181]. LIU G J, WANG Z J, WANG Y F, et al. Systematic assessment and meta-analysis of the efficacy and safety of fasudil in the treatment of cerebral vasospasm in patients with subarachnoid hemorrhage. Eur J Clin Pharmacol,

2012, 68(2): 131-139.

[182]. Guifang Cao, Chunxiang Yang, Hui Wang, Yang Sun, Yilu Xia.The effect of statins on the prevention of delayed cerebral vasospasm in subarachnoid hemorrhage patient: A meta-analysis. Stroke and Neurological Disease(Chinese)., 2008, 15(2): 111-113[164]

[183]. Kirkpatrick Peter J,Turner Carole L,Smith Christopher et al. Simvastatin in aneurysmal subarachnoid haemorrhage (STASH): a multicentre randomised phase 3 trial. Lancet Neurol, 2014, 13: 666-75.

[184]. McGirt Matthew J,Garces Ambrossi Giannina L,Huang Judy et al. Simvastatin for the prevention of symptomatic cerebral vasospasm following aneurysmal subarachnoid hemorrhage: a single-institution prospective cohort study. J. Neurosurg., 2009, 110: 968-74.

[185]. Hui Sun, Yuli Hou, Linlin Cui, Qiuyun Niu. Efficacy and safety of clazosentan for cerebral vasospasm after aneurysmal subarachnoid hemorrhage：a systematic review. Chinese Journal of Clinicians (Electronic Edition), 2016, 19: 2887-2891.

[186]. BECK J, RAABE A. Clazosentan: prevention of cerebral vasospasm and the potential to overcome infarction. Acta Neurochir Suppl, 2011, 110: 147-150.

[187]. FUJIMURA M, JOO J Y, KIM J S, et al. Preventive Effect of Clazosentan against Cerebral Vasospasm after Clipping Surgery for Aneurysmal Subarachnoid Hemorrhage in Japanese and Korean Patients. Cerebrovasc

Dis, 2017, 44(1-2): 59-67.

[188]. Macdonald R Loch,Higashida Randall T,Keller Emanuela et al. Clazosentan, an endothelin receptor antagonist, in patients with aneurysmal subarachnoid haemorrhage undergoing surgical clipping: a randomised, double-blind, placebo-controlled phase 3 trial (CONSCIOUS-2).Lancet Neurol, 2011, 10: 618-25.

[189]. Macdonald R Loch,Higashida Randall T,Keller Emanuela et al. Randomized trial of clazosentan in patients with aneurysmal subarachnoid hemorrhage undergoing endovascular coiling.[J] .Stroke, 2012, 43: 1463-9.

[190]. JANG YG, ILODIGWE D, MACDONALD R L. Meta-analysis of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage. Neurocrit Care, 2009, 10(1): 141-147.

[191]. SCHMID-ELSAESSER R, KUNZ M, ZAUSINGER S, et al. Intravenous magnesium versus nimodipine in the treatment of patients with aneurysmal subarachnoid hemorrhage: a randomized study. Neurosurgery, 2006, 58(6): 1054-1065.

[192]. Dorhout Mees Sanne M,Algra Ale,Vandertop W Peter et al. Magnesium for aneurysmal subarachnoid haemorrhage (MASH-2): a randomised placebo-controlled trial.Lancet, 2012, 380: 44-9.

[193]. SUZUKI S, SAYAMA T, NAKAMURA T, et al. Cilostazol improves outcome after subarachnoid hemorrhage: a preliminary report. Cerebrovasc Dis,

2011, 32(1): 89-93.

[194]. MUNAKATA A, OHKUMA H, NAKANO T, et al. Effect of a free radical scavenger, edaravone, in the treatment of patients with aneurysmal subarachnoid hemorrhage. Neurosurgery, 2009, 64(3): 423-428.

[195]. Yunchun Wang. The effect of edaravone in the prevention and treatment of cerebral vasospasm after subarachnoid hemorrhage. Chinese Journal of Gerontology(Chinese). 2010, 30(6): 829-830

[196]. WURM G, TOMANCOK B, NUSSBAUMER K, et al. Reduction of ischemic sequelae following spontaneous subarachnoid hemorrhage: a double-blind, randomized comparison of enoxaparin versus placebo. Clin Neurol Neurosurg, 2004, 106(2): 97-103.

[197]. Yonghui Zhu. Clinical Study of Flunarizine Hydrochloride in Preventing and Treating Cerebral Vasospasm after Subarachnoid Hemorrhage. Chinese Journal of Integrative Medicine on Cardio-/Cerebrovascular Disease, 2005, 3(2): 120-121

[198]. Yuanyuan Zhao, Jianlin Xu, Lin Lou. Effect of alprostadil combined with nimodipine to prevent symptomatic cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Chinese Journal of Clinical Pharmacy(Chinese). 2015, 24(1):4-8

**Supplemental Table 1 Ottawa headache Rule**

| **Red-flag clinical symptoms suggesting SAH** |
|---|
| Onset greater than or equal to 40 years |
| Presence of neck pain or stiffness |
| Witnessed loss of consciousness |
| Onset during exertion |
| Thunder clap headache (pain peaking within 1 s) |
| Limited neck flexion on exam |

**Supplemental Table 2 Hunt-Hess Scale[48]**

| Grade | Clinical description | Survival/% |
|---|---|---|
| 0 | Unruptured aneurysm | — |
| 1 | Asymptomatic or minimal headache and slight nuchal rigidity | 70 |
| 2 | Moderate to severe headache, nuchal rigidity, but no neurological deficit other than cranial nerve palsy | 60 |
| 3 | Drowsiness, confusion, or mild focal deficit | 50 |
| 4 | Stupor, mild or severe hemiparesis, possible early decerebrate rigidity, vegetative disturbance | 20 |
| 5 | Deep coma, decerebrate rigidity, moribund appearance | 10 |

*Serious systemic disease such as hypertension, diabetes, severe arteriosclerosis, chronic pulmonary disease seen on arteriography

result in assignment of the patient to the less favorable category

**Supplemental Table 3 WFNS Grading Scale[48]**

| Grade | Description |
|---|---|
| I | GCS 15, no motor deficit |
| II | GCS 13-14 without deficit |
| III | GCS 13-14 with focal neurological deficit |
| IV | GCS 7-12, with or without deficit |
| V | GCS 3-6, with or without deficit |

**Supplemental Table 4 Fisher Grading Scale[49]**

| Grade | CT Scan Appearance | Incidence of Symptomatic Vasospasm/% |
|---|---|---|
| 1 | No blood detected | 21 |
| 2 | Diffuse deposition of subarachnoid blood, no clots | 25 |
| 3 | Localized clots or dense deposition of subarachnoid blood >1 mm thick in the vertical plane (interhemispheric fissure, insular cistern, or ambient cistern) or >5×3mm in longitudinal and transverse dimension in horizontal plane (stem of sylvian fissure, sylvian cistern or interpeduncular cistern) | 37 |
| 4 | Diffuse or no subarachnoid blood, but intracerebral or intraventricular clots are present | 31 |

**Supplemental Table 5 Modified Fisher Grading Scale[50]**

| Grade | CT Scan Appearance | Incidence of Symptomatic Vasospasm/% |
|---|---|---|
| 0 | No SAH or IVH | 0 |
| 1 | Focal or diffuse thin layer of SAH <1mm in depth, no IVH | 24 |
| 2 | Focal or diffuse thin layer of SAH <1mm in depth, IVH present | 33 |
| 3 | Focal or diffuse thick layer of SAH >1mm in depth, no IVH | 33 |
| 4 | Focal or diffuse thick layer of SAH >1mm in depth, IVH present | 40 |

*SAH, subarachnoid hemorrhage; IVH, intraventricular hemorrhage

**Supplemental Table 6 Claassen Grading Scale[52]**

| Grade | Description |
|---|---|
| 0 | No SAH or IVH |
| 1 | Minimal/thin SAH, no IVH in either lateral ventricle |
| 2 | Minimal/thin SAH, with IVH in both lateral ventricle |
| 3 | Dense SAH, no IVH in either lateral ventricle |
| 4 | Dense SAH, with IVH in both lateral ventricle |

*SAH, subarachnoid hemorrhage; IVH, intraventricular hemorrhage

**Supplemental Table 7 BNI Grading Scale[54]**

| Grade | Maximum SAH Thickness measured perpendicular to the direction of cistern or fissure |
|---|---|
| 1 | No visible SAH |
| 2 | ≤5mm |
| 3 | 6～10mm |
| 4 | 11～15mm |
| 5 | 16～20mm |

* BNI ≥ 3 points have a higher risk of shunt-dependent hydrocephalus

**Supplemental Table 8 SDASH Score[55]**

| Item | Score | |
|---|---|---|
| Presence of Acute Hydrocephalus | No：0 | Yes：2 |
| BNI Score | 1～2：0 | 3～5：1 |
| Hunt-Hess Grade | 1～3：0 | 4～5：1 |

*The SDASH score ranges from 0 to 4 points, and 0 to 4 points corresponding to the shunt dependent hydrocephalus were 2.9%, 18.6%, 40.6%, 50% and 76.2%, respectively.

**Supplemental Table 9 List of agents to prevent CVS and DCI**

| Agents | Research design | Researcher (year) | Sample size | Intervention | Control | Research result |
|---|---|---|---|---|---|---|
| Nimodipine | Meta analysis | Liu et al. (2011) [179] | 8 RCTs, 1499 pts | Nimodipine | Placebo | Reduced the risk of symptomatic CVS (*OR* = 0.54 , 95% *CI* 0.42-0.69).<br>No increase the risk of adverse events and rebleeding rate |
| | Dosage: One domestic study result showed that the application of high-moderated dosage [(1 *to* 2 mg/h) and (0.5 *to* 0.8 mg/h)] of nimodipine might significantly improve the treatment efficiency of patients with CVS after SAH, compared to that of low dose [180]. | | | | | |
| Fasudil | Meta-analysis | Liu GJ. et al (2012) [181] | 8 prospective controlled studies | Fasudil | Nimodipine placebo | Reduced the risk of symptomatic CVS (*OR* = 0.48, 95% *CI* 0.32-0.72),<br>Reduced the risk of cerebral infarction (*OR* =0.50, 95% *CI* 0.34-0.76) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | (6 of them were RCTs) | | | |
| Statins | Meta-analysis | Cao GF, et al. (2008)[182] | 5 RCTs | Statins | Standard treatment | Significantly reduced risk of DCI (*OR* =0.34,95% *CI* 0.20-0.60)<br>No reduction rate of mortality (*OR* =0.67,95%*CI* 0.33-1.39) |
| | RCT | STASH Kirkpatrick et al. (2014) [183] | 1 RCT | simvastatin 40mg | placebo | No improvement of the mRS distribution (OR 0·97, 95% CI 0·75–1·25; p=0·803<br>No reduction of mortality at 6 month（log-rank p=0·592） |
| | Cohort | McGirt et al（2009） [184] | 1 Cohort 340 patients | Simvastatin | Standard treatment | No differences in the incidence of CVS (25.3 vs 30.5%; p = 0.277), in-hospital mortality rate (18 vs 15%; p = 0.468), length of hospitalization (21 +/- 15 vs 19 +/- 12 days; p = |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | 0.281), or poor outcome at discharge (Glasgow Outcome Scale Scores 1-2: 21.7 vs 18.2%; p = 0.416). |
| Clazosentan | Meta-analysis | Sun H, et al. (2016) [185] | .4 RCTs 2161 pts | Clazosentan | Standard treatment | Significantly decreased vasospasm (*RR* 0.58, 95% *CI* 0.48-0.71) and vasospasm-related cerebral infarction (*RR* =0. 79,95% *CI* 0.63-1.00) Note: increased pulmonary complications, anemia, hypotension |
| | RCT | Beck J, et al. (2011)[186] | 413 patients | Clazosentan | Placebo | Significantly reduced the incidence of cerebral vasospasm and this effect was dose-dependent and may be reduced at the highest dose 65% of cerebral vasospasm incidence |
| | RCT | Fujimura M, et al. (2017)[187] | 158 Japanese and Korean patients after | Clazosentan | Placebo | Significantly reduced cerebral vasospasm and DCI. Preferred dosage as 10mg/h. |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | clipping surgery | | | |
| | RCT | CONSCIOUS-2 Macdonald, et al.(2011) [188] | 1157 aSAH patients secured by surgical clipping | Clazosentan 5 mg/h | Placebo | No significant on the composite endpoint (week 6) included all-cause mortality, vasospasm-related new cerebral infarcts, delayed ischemic neurological deficit due to vasospasm, and rescue therapy for vasospasm (relative risk reduction 17%, 95% CI –4 to 33; p=0·10) |
| | RCT | CONSCIOUS-3 Macdonald R, et al. (2012) [189] | 517 | Clazosentan 5mg/h 15 mg/h | placebo | Clazosentan 15mg/h was significantly reduced post-aSAH vasospasm-related morbidity/all-cause mortality (when 5mg/h OR 0.786; 95% CI, 0.479–1.289; P=0.340, when 15mg/h OR, 0.474; 95% CI, 0.275–0.818; P=0.007) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Tirilazad | Meta-analysis | JANG YG, et al. (2009)[190]] | 5 RCTs 3797 pts | Tirilazad | Placebo | Significantly reduced the risk of symptomatic vasospasm (*OR*=0.80, 95% *CI* 0.69 - 0.93) Reduced cerebral infarction risk (*OR*=1.04, 95% *CI*:0.89 ~ 1.22) Improved GOS score without statistic difference (*OR*=1.04,95%*CI* 0.89-1.20) |
| Magnesium sulfate | ● Two large-sample RCTs both found that intravenous magnesium sulfate had no effect not only on the risk reduction of CVS and DCI, but also not improve clinical outcome as well [191,192]. | | | | | |
| Cilostazol | ● One preliminary study showed that cilostazol was not associated with CVS and DCI reduction, compared to that of nimodipine alone. However, there was an underlying improvement of modified Rankin Scale [193]. | | | | | |
| Edaravone | ● One domestic controlled study and a Japanese RCT both found that the combined with edaravone was associated with a significant reduction of CVS and DCI [194,195] | | | | | |

| | |
|---|---|
| LMWH | ● A large randomized, double-blind, placebo-controlled study showed subcutaneous injection LMWH (20mg/kg, qd) for 3 weeks could significantly reduce rate of DCI and CVS, which suggested an improvement of overall prognosis [196] |
| Flunarizine, | ● One domestic RCT reported that standard treatment combined with flunarizine could significantly reduce the rate of CVS[197]. |
| Alprostadil | ● One domestic RCT reported combined with Alprostadil could significantly reduce the incidence of CVS after SAH, compared with standard therapy [198]. |

CVS: cerebral vasospasm symdrome; RCT: randomized controlled study; DCI: delayed cerebral infarction; LMWH: low molecular weighted heparin。