

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 ≥ 5 mm, but when the diameter of an aneurysm is < 5 mm, the sensitivity decreases to 64%-83% [22-23]. Previous studies have suggested that aneurysms < 3 mm in diameter is unreliably demonstrated on CTA [24-25]. It has been reported that the sensitivity of CTA for aneurysms with diameter < 4 mm is 92.3%, and when the diameter of aneurysm is ≥ 4 mm, 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% \sim 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 led 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 administered 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 administered 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 mellitus 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 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.

Recommendation 1. 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. Fasudil 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 of CVS (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.

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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]

Grad	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). 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), 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 ($OR = 0.34, 95\% CI 0.20-0.60$) 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 ($OR 0.97, 95\% CI 0.75-1.25; p=0.803$) 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 (<i>RR</i> 0.58, 95% <i>CI</i> 0.48-0.71) and vasospasm-related cerebral infarction (<i>RR</i> =0.79, 95% <i>CI</i> 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] ¹	5 RCTs 3797 pts	Tirilazad	Placebo	Significantly reduced the risk of symptomatic vasospasm (<i>OR</i> =0.80, 95% <i>CI</i> 0.69- 0.93) Reduced cerebral infarction risk (<i>OR</i> =1.04, 95% <i>CI</i> :0.89 ~ 1.22) Improved GOS score without statistic difference (<i>OR</i> =1.04,95% <i>CI</i> 0.89-1.20)
Magnesium sulfate	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none">● 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,	<ul style="list-style-type: none">● One domestic RCT reported that standard treatment combined with flunarizine could significantly reduce the rate of CVS[197].
Alprostadil	<ul style="list-style-type: none">● One domestic RCT reported combined with Alprostadil could significantly reduce the incidence of CVS after SAH, compared with standard therapy [198].

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