Emergency Neurological Life Support: Subarachnoid Hemorrhage

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Abstract

Subarachnoid hemorrhage (SAH) is a neurological emergency. Prompt recognition, expedited transport to an expert center, and early definitive care for sources of bleeding can improve patient outcomes. In patients with a normal mental status, the initial diagnosis can sometimes be challenging. The mainstay approach remains non-contrast head computed tomography (CT) followed by lumbar puncture when CT is non-diagnostic. Non-traumatic SAH is frequently due to aneurysmal bleeding, and the early care of patients should focus on identifying the source of hemorrhage, limiting the risk of re-rupture, limiting secondary brain injury, preventing development of hydrocephalus and securing the aneurysm with coiling or clipping. The management of blood pressure, hydrocephalus, cardiac output, and pain is crucial to maximizing the chances of a good outcome. Nimodipine should be initiated within 24 hours of aneurysmal SAH (aSAH). Early consideration of transfer to a comprehensive stroke center with a sufficient volume of aneurysm cases is warranted.

Key words: Subarachnoid hemorrhage, Aneurysm, Neurocritical care, Hydrocephalus, Vasospasm

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1 Introduction

Subarachnoid hemorrhage (SAH) is a neurological emergency with significant morbidity and mortality. The worldwide incidence of SAH ranges from 2 to 16 per 100,000 people which has remained stable over the past three decades. Although head trauma is the most common cause of blood in the subarachnoid space, this protocol will focus on non-traumatic SAH. In the United States, nontraumatic subarachnoid hemorrhage (SAH) accounts for about 3% of all strokes; majority (~80%) of which are due to rupture of intracranial aneurysms, 5% cases are due to other defined etiologies (e.g., arteriovenous malformation, vasculitis), and approximately 15% of cases with no identifiable source of hemorrhage. Given the predominance of aneurysmal rupture as the cause of SAH, we will primarily focus on workup and acute management of aneurysmal SAH (aSAH).

Updated guidelines by the Neurocritical Care Society (NCS) in 2011

and the American Heart Association (AHA)/American Stroke Association (ASA) in 2012 discuss the diagnosis and management of aneurysmal SAH upon presentation to the emergency department (ED) and provide an evidence-based review of SAH management.[1,2] The goal of ENLS is to address the initial management of SAH within the first few hours and will focus on establishing the diagnosis, administering urgent interventions, and communicating effectively with other treating clinicians. This module will give a broad framework and can be adapted to reflect global and regional variations based on the local availability of diagnostic tools and treatments.

A list of goals to accomplish in the first hour is listed in Table 1.

TABLE 1
Subarachnoid Hemorrhage Checklist for the First Hour

Checklist	
☐	Airway, breathing, circulation
☐	Head computed tomography (CT)
☐	Labs: PT/INR, PTT, CBC, chemistries, troponin, toxicology screen
☐	12 Lead ECG
☐	Target SBP goal <160mmHg
☐	Consult neurosurgery/ NCC team
☐	Address hydrocephalus if present

2 Diagnosis

Clinical Presentation

Case 1: A 56 year-old female smoker with history of hypertension had a sudden onset worst headache of her life that woke her up from sleep .Upon arrival to the ED, she was drowsy and reported severe headache, nausea and photophobia but clinical exam revealed no focal neurological deficit. Her blood pressure was 185/92 mm Hg. Non-contrast CT of the head showed dense SAH, predominantly in the anterior interhemispheric fissure, and bilateral sylvian fissures. No intraventricular hemorrhage or hydrocephalus was noted.

CT angiogram revealed the presence of anterior communicating artery aneurysm

Most patients with aneurysmal SAH experience the abrupt onset of a severe headache, which may be associated with vomiting, neck pain, neck stiffness, or loss of consciousness. Patients often describe this as the "worst headache of my life." The headache is often referred to as a thunderclap headache, which has a differential diagnosis beyond SAH.[3,4] In patients with known history of headaches, the acute headache is almost always more severe and more rapid in its pace of onset compared to prior headaches. In approximately 50% of patients, mental status is normal, and there are no focal neurological deficits. The remaining 50% of patients present with a broad spectrum of neurological deficits ranging from minor alteration in mental status to focal deficits, or in severe cases, coma.

Although the classic presentation of SAH includes the onset of a thunderclap headache with exertion or Valsalva maneuver, this presentation (headache developing with exertion) only occurs in a minority of patients, some of whom develop symptoms during sleep.[5,6] Some patients with alterations in mental status may not be able to provide a cogent history of the headache onset while others may present in coma. A small subset of patients may report headaches that did not begin suddenly. In about 10-40% of aSAH patients, the acute presenting headache is preceded by a warning aneurysmal leak leading to 'sentinel headache' which typically occurs about 2-8 weeks prior to overt aSAH. It is important to note that a therapeutic response to any type of analgesic, including a triptan that is often used for migraine headaches, should not be interpreted as evidence of a benign etiology.[7,8]

Approximately 5% of ED patients with SAH presenting with headache are misdiagnosed on their first visit.[9] Well-appearing patients with normal neurological exams may be mistaken to have a migraine or "sinus headache".[3,10] In one study, the most common reason for misdiagnosis was failure to perform a head CT scan.[11] Patients with smaller hemorrhages and normal mental status at presentation are often misdiagnosed, which can lead to worse outcomes.[3,10,11] Among neurologically intact patients, clinicians should strongly consider further diagnostic evaluation if the headache is abrupt in onset, more severe than any prior headache, and/or unique in character. One large prospective multicenter derivation cohort of 1999 patients suggested a set of clinical criteria to guide further workup for SAH in patients presenting with acute severe headache without neurologic deficit. The characteristics found to be predictive of aSAH included age > 40 years, witnessed loss of consciousness, complaint of neck pain or stiffness, onset with exertion, arrival by ambulance, vomiting, diastolic blood pressure ≥100 mm Hg or systolic blood pressure ≥160 mm Hg.[12] This study was subsequently validated in a multi-center cohort of 2,131 adults presenting to the ED with headache peaking within one hour and no neurologic deficits. This validation cohort found that the best model to predict subarachnoid hemorrhage with highest sensitivity of 98.5% (95% CI, 94.6%-99.6%) and specificity of 27.6% (95% CI, 25.7%-29.6%) included age >40 years, neck pain or stiffness, witnessed loss of consciousness, and onset during exertion (set of rules used in derivation cohort).[79] However, the investigators also noted that the addition of two more variables including thunderclap headache (instantly peaking pain within one second) and limited neck flexion on examination (defined as inability to touch chin to chest or raise the head 8 cm off the bed if supine), resulted in a sensitivity of 100% (95% CI, 97.2%-100.0%) with specificity of 15.3% (95% CI, 13.8%-16.9%). The set of these 6 clinical variables was designated the "Ottawa SAH Rule" with clinical applicability in patients older than 15 years with new severe non-traumatic headache reaching maximum intensity within one hour. Further val-

idation of the "Ottawa SAH Rule" in a multi-center cohort of 1,153 neurologically intact adult patients with a headache peaking within one hour of onset suggested that the Ottawa SAH Rule had 100% sensitivity (95% CI 94.6%–100%) with a specificity of 13.6% (95% CI 13.1%–15.8%). In patients with all negative criteria and low pre-test probability, further testing may be avoided.[74] An additional clinical decision rule with inclusion of lab variables has also been proposed.

Some of the presenting signs and symptoms of SAH may mimic alternate diagnoses.[3,10] Some examples include:

- Isolated neck pain (cervical muscle strain or degenerative arthritis)
- Fever and headache (viral syndrome or meningitis)
- Prominent nausea and vomiting (gastroenteritis – note the absence of diarrhea)
- Elevated blood pressure (BP) or electrocardiographic abnormalities (hypertensive encephalopathy or acute coronary syndrome)

In other situations, a specific clinical finding, such as a third nerve palsy or an ocular hemorrhage in the sub-hyaloid space, may suggest the diagnosis of SAH. All patients with a new severe headache and a new abnormality in their neurological exam should undergo prompt neuroimaging with a CT scan upon presentation.

3 Prehospital Care

A variety of prehospital neurological examination tools, including the Cincinnati Prehospital Stroke Scale, Los Angeles Prehospital Stroke Screen, National Institutes of Health Stroke Scale, Miami Emergency Neurological Deficit Scale, and Glasgow Coma Scale, are used by emergency medical services personnel.[13,14] For patients presenting with isolated headache who are neurologically intact, there are no specific prehospital interventions, apart from consideration of analgesics. For patients presenting with a headache and neurological deficits, pre-notification of the ED staff about the neurological deficits and the finger stick glucose are important first steps. Patients who are severely encephalopathic, comatose, or vomiting repeatedly may need to have their airway protected by endotracheal intubation in the field. Admission of patients with SAH to low-volume centers is known to be associated with higher mortality while those with high volume centers are more likely to have a favorable discharge disposition.[15,39,40] Hence transfer of the patient to a high-volume center with availability of multidisciplinary neurointensive care services, vascular neurosurgeons and endovascular specialists is recommended.

4 Airway and Hemodynamic Management

The decision to perform endotracheal intubation is based on the inability of the patient to protect their airway, increased work of breathing, hypoxia resistant to supplemental oxygen, or anticipated clinical decompensation, especially if transfer to another facility is planned (see the *ENLS Airway, Ventilation, and Sedation* protocol). Clinicians should be prepared to intubate at any time, given that the neurological examination can decline rapidly, particularly in the setting of aneurysm re-rupture, acute hydrocephalus, or herniation. Cardiovascular resuscitation should be performed, if necessary, in accordance with

Advanced Cardiovascular Life Support guidelines.[13,14]

5 Initial Clinical Evaluation

After initial stabilization, a thorough history should be obtained from the patient or a witness to the event for those patients who are unable to provide their own history. A comprehensive clinical examination should be performed including general systemic and focused neurological examination. Focused clinical evaluation for SAH includes determination of level of consciousness (e.g., assessment of mental status, Glasgow coma scale), ocular and pupillary exam including funduscopic evaluation to assess for any ocular subhyaloid hemorrhage, determination of meningeal signs, and assessment of potential focal neurological deficits including cranial nerve dysfunction.

Several grading systems have been developed to correlate the presenting clinical status of the patient with long-term neurologic outcome. The most commonly used clinical grading systems include (i) the Hunt–Hess classification and (ii) the World Federation of Neurosurgical Societies classification (Table 2). In both the grading systems, impairment of consciousness increases with higher grade and is the major determinant of clinical outcome.

Table 2
World Federation of Neurosurgical Societies Classification

Severity	Hunt and Hess Scale	WFNS
Grade 1	Asymptomatic or mild headache and mild nuchal rigidity (if present). Alert and Oriented	GCS 15
Grade 2	Moderate to severe headache, nuchal rigidity, no focal neurologic deficit other than cranial nerve palsy	GCS 14-13 without major focal deficit such as aphasia, hemiparesis or hemiplegia
Grade 3	Drowsiness, confusion, lethargy or mild focal neurology deficit other than cranial nerve palsy	GCS 14-13 with major focal neurologic deficit
Grade 4	Stupor or moderate to severe focal deficit/hemiparesis	FCS 12-7 with or without major focal neurologic deficit
Grade 5	Coma, extensor posturing, moribund appearance	GCS 6-3 with or without major focal deficit

These clinical scores predict mortality with level of impaired consciousness as the most important predictor of mortality. WFNS: World Federation of Neurological Surgeons; GCS: Glasgow Come Scale

6 Radiographic Presentation

Case 3: A 55-year-old male presents to the Emergency Department with a sudden onset of severe headache and associated nausea. He was watching TV at home when he developed the headache. He has no known past medical history and his neurological exam is intact. A non-contrasted CT of the brain reveals no acute abnormality.

After a thorough history and physical examination, the next step in diagnosis of SAH in the ED is with a non-contrast head CT.[2,3,10] The CT in patients with aneurysmal SAH

will show blood, which appears hyperdense (i.e., brighter than brain tissue) in the subarachnoid space. The distribution of the blood is usually dependent on the location of the aneurysm/underlying lesion but is typically located in the basal cisterns around the circle of Willis, major fissures, and within the ventricles. Occasionally, only intraventricular blood is seen. Subarachnoid blood that is present only in the sulci along the convexity is typically due to non-aneurysmal causes, most commonly head trauma. Less common causes include AVMs, cerebral amyloid angiopathy, reversible cerebral vasoconstriction syndrome, vasculitis, and other toxic and inflammatory vasculopathies.[19,20]

In patients with aSAH, several radiological grades have been developed based on the severity of SAH on the CT scan, which is the most important predictor for development of vasospasm and delayed cerebral ischemia (DCI)/cerebral infarction. The most commonly used radiological grades include (i) The Fisher Grading Scale and (ii) the modified Fisher Grading Scale (Table 3). In the original Fisher scale, the highest risk of vasospasm occurred in grade 3 (grade = 1 to 4). The modified Fisher Scale was subsequently adapted from the original Fisher Scale to ensure correlation of higher grades with higher likelihood of vasospasm/delayed cerebral ischemia (DCI, grade 0 to 4).[42,43]

Table 3
Modified Fisher Grading Scale

Severity	Fisher Scale	Modified Fisher Scale
Grade 1		No SAH or IVH
Grade 2	No SAH or IVH	Localized of diffuse thin SAH without IVH
Grade 3	Diffuse 'thin' SAH with all vertical layers <1mm in thickness	No or, localized or diffuse 'thin' SAH with IVH
Grade 4	'Thick' vertical layers of blood measuring ≥1mm in thickness or localized clots (>3x5mm)	Localized or diffuse 'thick' SAH with no IVH
Grade 5	Diffuse or no SAH but with ICH or IVH	Localized or diffuse 'thick'SAH with IVH

The severity of SAH and IVH on the presenting CT scan is the most important factor predicting delayed cerebral ischemia and cerebral infarction with important prognostic implications SAH: subarachnoid hemorrhage; IVH: intraventricular hemorrhage

Normal CT scans can occur in several settings. The two most important are (i) hemorrhages too small to be detectable by CT, and (ii) hemorrhages that have occurred days earlier, before the CT scan. The first factor is self-evident. The second, timing bias, is due to the normal circulation of cerebrospinal fluid (CSF), which may clear the SAH. The normal volume of CSF present in the dural compartment (150 ml) is replaced three times daily. As a result, the sensitivity of head CT for SAH decreases as time elapses.[8] Other possibilities include incorrect interpretation (CT is actually positive), a hematocrit ≤ 30% (blood is isodense with brain), and technical limitations (e.g., poor CT quality).[3,10]

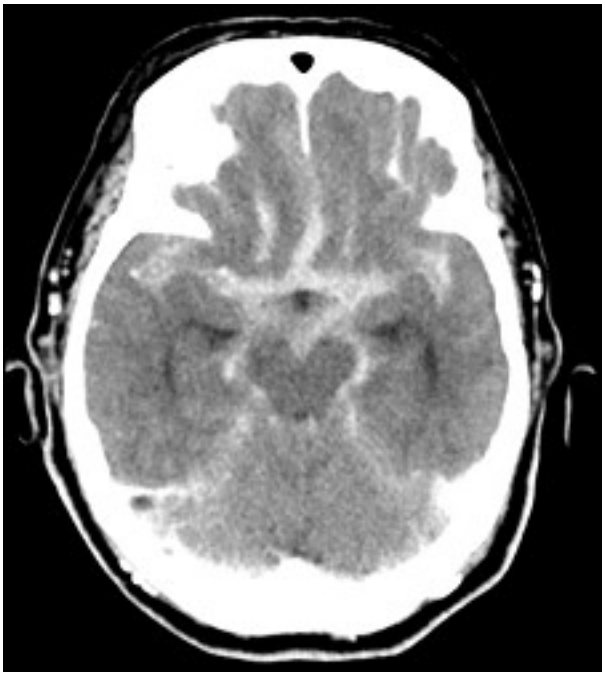


FIGURE 1
CT Brain with SAH

Studies relying on older CT technology suggest that CT sensitivity is close to 100% within the first three days of the hemorrhage, falls to 60–85% on day 5, and is approximately 50% at one week. Modern scanners are likely to provide more sensitive imaging. In a prospective, multicenter study on non-traumatic headache reaching maximum intensity within one hour, use of third generation, multidetector CT scanners with imaging interpretation by qualified radiologists showed the sensitivity of CT scan to be 100% in patients scanned within 6 hours of symptom onset.[21] Subsequent implementation study evaluating sensitivity of 6-hour CT suggested high sensitivity of 95.5% for SAH detection.[22] However, in one retrospective study using multi-detector scanners, CT sensitivity for SAH in patients with normal mental status was reported to be only 91%, although timing of CT acquisition from symptom onset was not clear in this study.[21]

7 CT Negative for SAH/Lumbar Puncture Positive

Based on current evidence, patients being evaluated for SAH whose CT scans are negative, equivocal, or non-diagnostic should undergo lumbar puncture (LP).[1–3,10] As with CT, CSF results are also time-dependent. Large numbers of red blood cells (RBCs), generally in the thousands, are initially present but rapidly diminish with time due to the CSF circulatory cycle.

Xanthochromia, the yellowish discoloration of CSF that results from *in vivo* degradation of hemoglobin into bilirubin, oxyhemoglobin, and methemoglobin, begins to develop and is nearly universally present after 12 hours from the onset of the hemorrhage.[23] It can be detected by visual inspection of the centrifuged CSF or by spectrophotometry.

Although some experts recommend that spectrophotometry be used as a more sensitive method to detect xanthochromia, this method leads to a high proportion of false positives.[24] Nearly all hospital clinical laboratories use visual inspection following CSF centrifugation to assess xanthochromia.[25] Finally, CSF deemed "clear and colorless" by visual inspection is very unlikely to be compatible with SAH.[26] However, this visual inspection should be performed in a conical-base test tube (typically supplied in the LP kit) and not in a capillary tube. The tube of spinal fluid should be compared with water against a white background in neutral lighting. Measuring the opening pressure is recommended, because the presence of elevated opening pressure may also help to distinguish true SAH from a traumatic tap.[27]

In addition to measurement of the opening pressure and assessment for xanthochromia, a traumatic tap may be distinguished from SAH by comparing the number of RBCs present in the first tube of CSF as compared to the last. Whereas the number of RBCs will typically decrease from the first to the last tube in a traumatic tap, this does not exclude an aneurysmal SAH. A retrospective study of 1,739 patients with acute non-traumatic headache conducted in 12 Canadian EDs found that the presence of fewer than 2000 x 10^6/L RBCs in the final tube and the absence of xanthochromia had a negative predictive value of 100% (95% confidence interval 99.2 to 100%) for excluding SAH.[28]

8 Alternative Diagnostic Pathways

Other diagnostic pathways have been suggested, including the use of magnetic resonance imaging (MRI), which is highly sensitive for intracranial hemorrhage, including SAH. A systematic review and meta-analysis of MRI and time-of-flight MR angiography for detection of aneurysms reported a sensitivity of 95% (95% CI 89–98) with pooled specificity of 89% (80–95). For those patients presenting in a delayed fashion (weeks from symptom onset), hemosiderin-sensitive MRI sequences, such as susceptibility-weighted imaging and gradient echo T2*-weighted imaging could be useful for detecting SAH.[29–32] Given the widespread availability, lower cost, rapid acquisition, and greater experience with its interpretation, CT remains the recommended first test.[1–3] If MRI is used as the initial imaging test, LP is still necessary if the MRI is negative.[2]

Studies have proposed CT angiography (CTA) as the next best diagnostic step, instead of LP in patients with negative non-contrast head CT.[34–35] However, it is important to

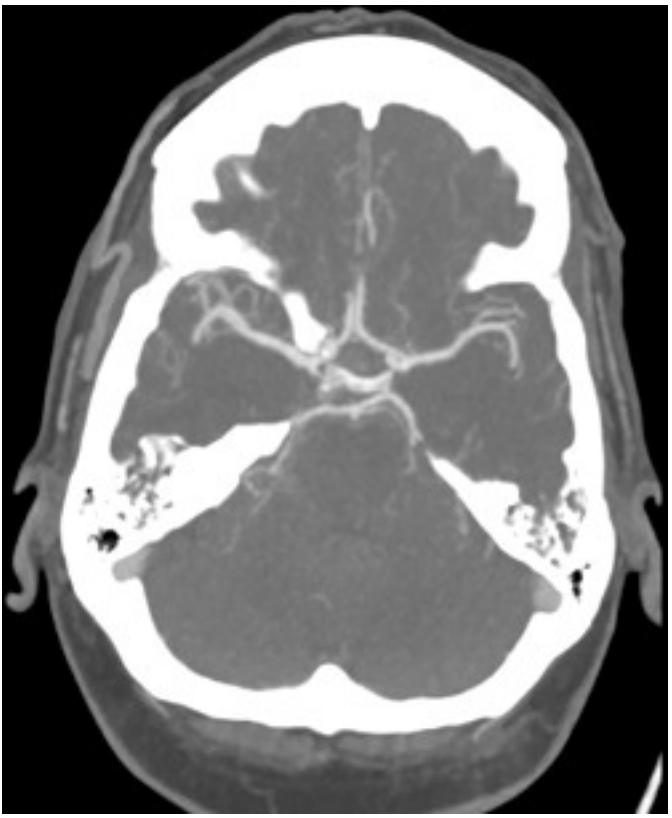


FIGURE 2

CT Angiogram demonstrating Circle of Willis

note that the function of an angiogram is to diagnose the presence of an aneurysm and not to detect SAH.[36] Given that the prevalence of aneurysms in the general population is 1-2%, detection of aneurysms by CTA may lead to management dilemma, especially in patients without imaging evidence of SAH where it would be difficult to ascertain rupture of the given aneurysm.[36] Downstream implications of this protocol should be considered in routine clinical practice and while developing institutional protocols for diagnosis of SAH.[36] However, CTA may be the appropriate next step in patients where LP cannot be obtained or those with very high pre-test probability for a ruptured aneurysm.

Furthermore, in patients whose diagnosis of SAH is confirmed by CT and/or LP, vascular imaging is still required to evaluate the source of hemorrhage. Although digital subtraction angiography (DSA) with three 3-dimensional (3D) reconstructions is considered the gold standard for detection of aneurysm and for surgical planning, CTA may be used in place of DSA where needed. A systematic review and meta-analysis evaluating the role of CTA using multi-detector CT scanner (majority of which was four-detector row scanner) in the diagnosis of cerebral aneurysm showed a pooled sensitivity of 98% (95% CI 95–98) with pooled specificity of 100% (95% CI: 97%, 100%), compared to DSA with or without 3-D reconstruction.[34]

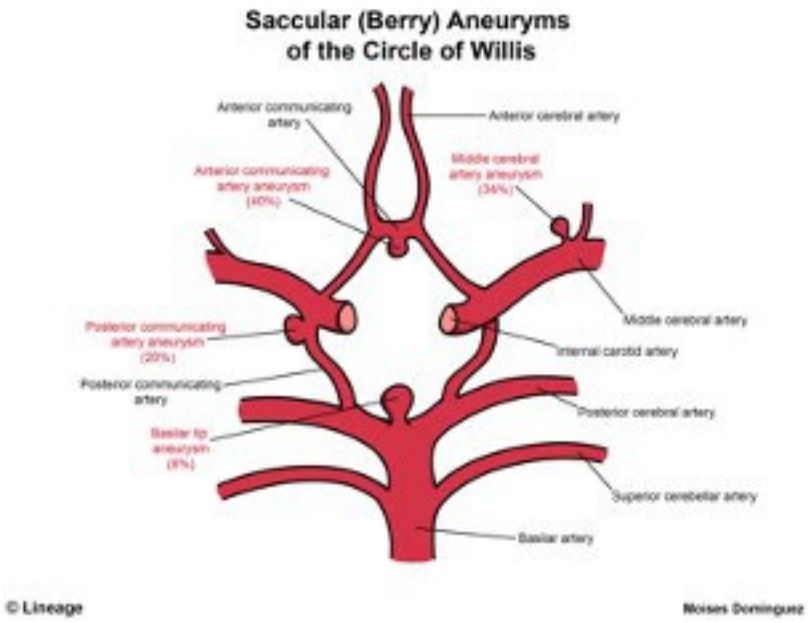


FIGURE 3

Classic locations of aneurysms

9 Initial Management of SAH

Once aSAH is confirmed, several management steps must be addressed. In addition to the specific steps below, the patient should be placed on bed rest with cardiac monitoring, and a 12–lead electrocardiogram should be obtained. Initial laboratory studies include a complete blood count as well as coagulation tests (PT, PTT, INR), electrolytes, renal function tests, troponin, and a type and screen. Urine should also be sent for a toxicology screen.

The risk of re-rupture is 4 to 14% in the first 24 hours after aSAH and remains elevated for 30 days, hence management strategies to mitigate the risk of re-rupture including treatment of severe hypertension is critical in the initial period. The aneurysm must be secured by isolating the aneurysm from the cerebrovascular circulation, either by surgical clipping or endovascular interventions including coiling. This should be carried out as soon as feasible, ideally within the first 24 hours of presentation.[1,2,37,38] Several studies have shown that patients have improved outcomes when they are treated at SAH high volume centers.[39,40] Low volume centers should strongly consider transfer of the patient to a high volume center as soon as feasible. Ideally, pre-arranged transfer agreements should be in place.

10 Communication

Upon diagnosis and clinical stabilization, the clinician should speak to a cerebrovascular specialist. When communicating with an accepting or referring clinician about the

patient, consider including the key elements listed in Table 4. In addition to the standard information about a patient's history and presentation, the communication should address airway status, clinical status of the patient (including clinical and radiological grades such as Hunt and Hess grade, WFNS and the Fisher or Modified Fisher scale as described above), CSF analysis, and presence or absence of hydrocephalus. The discussion should also include goals for BP control, review of administered medications for pain and anxiety, laboratory results (especially coagulation tests), seizure prophylaxis (please refer to section on Seizure Prophylaxis), available imaging studies as well as need for additional imaging as required. The role of acute (first hour) administration of nimodipine is unclear and requires placement of a feeding tube in patients who cannot swallow and placing a feeding tube can lead to retching or combativeness and may increase the risk of aneurysm re-rupture. For patients with hydrocephalus who are being transferred, it is reasonable to have a neurosurgeon place an EVD if it can be accomplished expeditiously. This is particularly important if the transport times are long, as the monitoring of the neurological exam of intubated SAH patients in transit can be limited. Community based neurosurgeons who may not manage SAH definitively, can potentially limit secondary brain damage by addressing acute hydrocephalus.

Table 4

Subarachnoid Hemorrhage Communication Regarding Assessment and Referral

Communication
☐ Airway status
☐ Hemodynamic status and blood pressure control (BP goals)
☐ Clinical presentation (level of consciousness, motor exam, pupils)
☐ WFNS score and Hunt-Hess Grade (if know)
☐ Imaging/ LP results
☐ Coagulopathy present?
☐ Hydrocephalus present?
☐ Medications given (dose and time administered), including sedatives, analgesics, seizure prophylaxis, anto0hypertensives, and nimodipine
☐ Coordination of other vascular imaging

11 Seizure Prophylaxis

Approximately 20% of SAH patients have seizures prior to hospital arrival, and another 5-10% experience seizure after admission.[44–45] Early seizures may increase the risk of aneurysm re-rupture and elevated intracranial pressure (ICP). Acute seizures should be treated with antiepileptic medications. In patients with persistent altered mental status, non-convulsive status epilepticus may be present, which can be diagnosed by the help of continuous electroencephalography (EEG).

Both the AHA and NCS guidelines suggest consideration of anti-seizure medications in the immediate post-hemorrhage period.[1,2] A very short course of prophylactic anti-seizure medications may be recommended in the period following diagnosis and before definitive aneurysm treatment because of a concern for seizure-related precipitation of aneurysm re-rupture. As phenytoin may lead to worse long-term cognitive outcomes, use of an alternative antiepileptic agent should be considered such as levetiracetam.[46]

12 Decline in Neurological Status

Some patients with SAH will experience an early deterioration in neurological status. It is important in these patients to consider the full differential diagnosis, since the causes, and thus treatments will vary. Reassessment of vital signs, cardiac telemetry monitoring, and the neurological exam are critical. New hypotension will decrease cerebral perfusion pressure. New hypoxia may result from neurogenic pulmonary edema. Arrhythmias may also lead to hypotension. Cardiovascular collapse could be the result of cerebral herniation

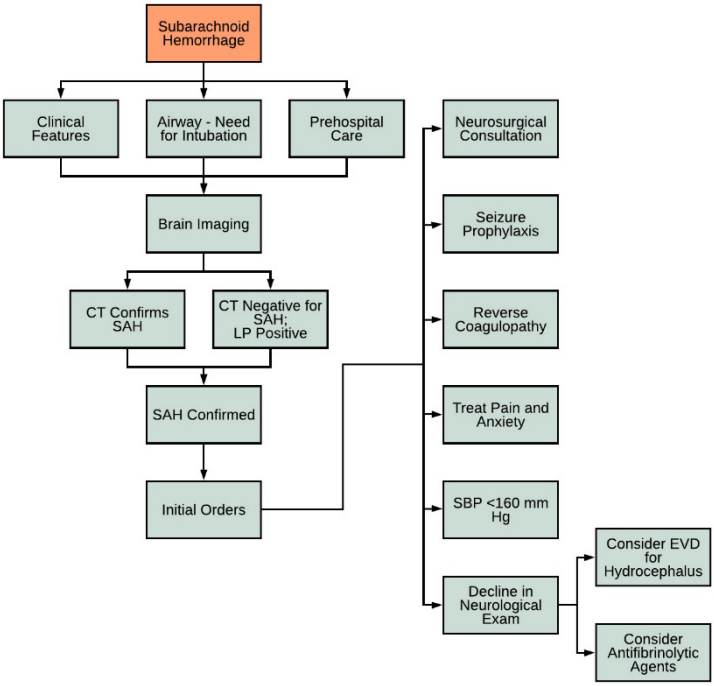


DIAGRAM 1
ENLS Subarachnoid Hemorrhage protocol

(Cushing's response), neurocardiogenic shock from stress induced cardiomyopathy, or respiratory failure from neurogenic pulmonary edema. Physical examination may show evidence of herniation or a new seizure requiring treatment.

A repeat CT scan is necessary, as it may show herniation, re-bleeding, development of or increase in hydrocephalus, or development of an intraparenchymal or subdural hematoma.

13 Coagulopathy

Coagulopathy should be urgently treated (see the algorithms in the *ENLS Pharmacology* protocol for more details). Patients taking Vitamin K antagonists including warfarin with an INR ≥ 1.4 should be treated with some combination of IV vitamin K (10 mg IV), and prothrombin complex concentrates (PCC).[47] Fresh Frozen Plasma (FFP) is an alternative for reversal if PCC is unavailable. Thrombocytopenia (platelets <100,000/microliter) can be treated with platelet transfusions (See the *ENLS Pharmacology* protocol regarding

reversal of factor Xa and thrombin inhibitors for details).

Oral antiplatelet agents, such as aspirin, clopidogrel, ticagrelor or prasugrel, can potentially increase the risk and severity of aneurysm re-rupture, as well as neurosurgical complications. Management recommendations were recently published by NCS and the Society of Critical Care Medicine (SCCM) in their 2016 Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage: platelet transfusion is recommended for patients with aspirin- or ADP inhibitor-associated SAH who will undergo a neurosurgical procedure, while platelet transfusion is *not* recommended if no neurosurgical procedure is planned.[47] The risk-benefit ratio of anti-platelet therapy reversal using other hemostatic agents such as desmopressin (DDAVP) should be considered for individual patients.

14 Pain and Anxiety

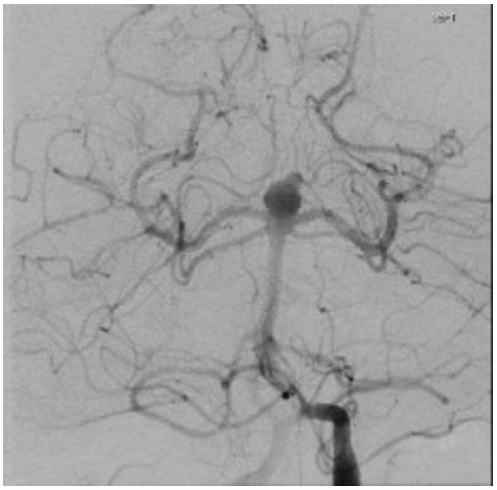
In addition to a primary goal of achieving the patient's comfort, treatment of pain, vomiting, and anxiety is clinically important. Judicious amounts of short-acting IV analgesics such as fentanyl should be used to treat pain. Treating vomiting with anti-emetics may also be helpful. If there is a significant component of anxiety, small intermittent doses of a benzodiazepine may be appropriate. All of these steps may also help to control a BP elevation related to pain and/or anxiety. Sedative and analgesic medications should be carefully titrated to avoid over-sedation, which can mask subtle mental status changes. Pharmacological reversal in the setting of over-sedation in these patients risks precipitating agitation, seizures and aneurysm re-rupture.

15 BP Management

AHA/ASA and NCS guidelines acknowledge the lack of quality data about BP control in SAH patients and suggest only that BP should be monitored and controlled to "balance the risk of stroke, hypertension-associated re-bleeding, and maintenance of the cerebral perfusion pressure".[1,2] Current guidelines suggest treating severe hypertension in patients with an unsecured ruptured aneurysm. Modest hypertension [mean arterial pressure (MAP) < 110 mmHg] may not require treatment. Pre-morbid BPs should be considered and used to inform the risks and benefits of treatment. Antihypertensive medications that are short acting, titratable, and can be administered as a continuous infusion, such as nicardipine, clevidipine, labetalol or urapidil to reduce the systolic pressure to <160 mmHg, or the MAP to < 110 mmHg, should be used, keeping in mind the principles mentioned above. Nitroprusside and nitroglycerine should be avoided because these agents may cause cerebrovascular dilation and thereby increase ICP.[48]

16 Hydrocephalus

The clinician should carefully evaluate the CT scan for hydrocephalus, which occurs in up to 30% of SAH patients in the first three days.[49,50] This may be asymptomatic but is more often seen in severely affected patients. If the hydrocephalus is symptomatic, it



can be treated with an EVD, although some data suggest that EVD placement may risk re-bleeding.[2] Additionally, comatose patients with hydrocephalus may have elevated ICP, so placement of an external ventricular drain (EVD) will not only reduce ICP via CSF diversion, but it will also provide a means to monitor ICP throughout transport or during hospitalization. Caution is needed to prevent over-drainage and pressure shifts during EVD placement and management prior to securing the aneurysm as this may increase the risk of aneurysm re-rupture.[97,98] Refer to the *ENLS Intracranial Hypertension and Herniation* protocol for further information.

FIGURE 4

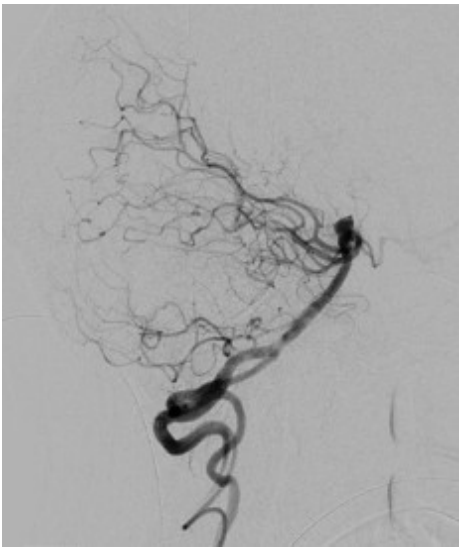


FIGURE 5

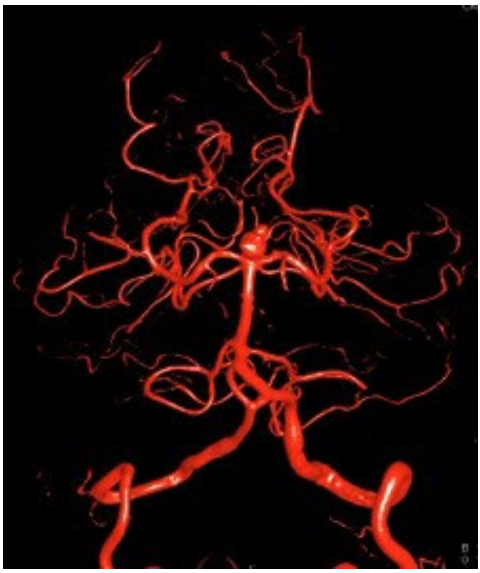


FIGURE 6:

17 Antifibrinolytic Agents

Prevention of rebleeding prior to definitive aneurysm treatment is an important goal. In the past, when surgical treatment was delayed, pre-operative antifibrinolytic treatment was standard. Currently, early definitive treatment of the aneurysm is recommended.[2] Thus, there has been an increased interest in early, short-term antifibrinolytic treatment with either epsilon aminocaproic acid or tranexamic acid (TXA) in situations where surgical or interventional options are not readily available. One study of administration of TXA to SAH patients, most of whom were treated with TXA within 24 hours, demonstrated an 80% reduction in re-bleeding before the definitive treatment.[51] Aneurysm re-rupture is often fatal, and since most re-ruptures occur within the first 12-24 hours of the initial hemorrhage, use of these procoagulant drugs for the first few days until aneurysm is secured may be an appropriate strategy.[52]

18 Management of Delayed Cerebral Ischemia

Delayed cerebral ischemia (DCI) is a clinical syndrome that occurs in patients with SAH resulting in decline in neurological status. Narrowing of angiographically visible intracranial vessels or vasospasm occurs in about 70% of patients with aSAH. It typically starts around day 3 after aneurysm rupture, peaks at about 7 to 10 days, and resolves by 14-21 days. However, in about 10% of patients, cerebral vasospasm can present as early angiographic vasospasm with spasm visible on admission. Furthermore, the patient may present in a delayed manner with acute vasospasm and risk for cerebral ischemia at the time of presentation. Despite the common belief that DCI is a result of vasospasm, DCI is only observed in less than half of patients with vasospasm and the focal neurological

deficit may occur independently, away from the region of apparent vasospasm, suggesting a role of various underlying vascular and neural factors.

The use of oral or enteral nimodipine has been shown in multiple randomized trials to improve outcomes of SAH patients, presumably by limiting DCI.[53–55] Nimodipine is a calcium channel blocker and is rapidly absorbed after oral administration, and peak concentrations are generally attained within one hour. Its precise mechanism of action in humans is unknown. Because nimodipine is administered orally or enterally, and many acute SAH patients cannot swallow, the administration of oral nimodipine is not listed as a priority in the first hour. If enteral nimodipine is not available, intravenous nimodipine may be considered.[56] The effect of nimodipine is not mediated by amelioration of angiographic vasospasm; rather, nimodipine works via a presumed cellular neuroprotective mechanism.

The presence of early vasospasm is an early predictor of DCI, commonly refractory to therapeutic intervention and has been associated with poor neurologic outcome. It is noted to be more common in patients with high grade SAH, history of SAH, presence of intracerebral or intraventricular hemorrhage, large aneurysms and fibromuscular dysplasia. Management of vasospasm prevention of DCI includes monitoring and detection of vasospasm and optimization of cerebral perfusion by ensuring euvolemia, normal hemoglobin, adequate blood pressure and intra-arterial spasmolysis when/where needed. Routine screening of large artery vasospasm using transcranial Doppler ultrasonography (TCD) is recommended. Although TCD sensitivities have varied across studies, a recent meta-analysis has suggested reasonable sensitivity of ~90% with specificity of 71% of this non-invasive portable technology for detection of vasospasm.[75] Use of CTA for vasospasm detection is reasonable although DSA is the gold standard for detection of large artery spasm. The use of CT or MR perfusion images can help assess regions of hypoperfusion and cerebral ischemia.

Prevention of vasospasm and DCI includes administration of nimodipine from the time of presentation, as is clinically feasible, until day 21.[53–56] Maintenance of euvolemia and hemoglobin of 8-10 g/dl is recommended, although the optimal hemoglobin concentration has not been determined. In patients with clinical suspicion of DCI, a trial of induced hypertension is recommended. Milrinone may have a role as an adjunct to vasopressors in patients with vasospasm.[76] If DCI is noted in the territory of a major cerebral artery spasm, DSA with cerebral angioplasty and/or selective intraarterial vasodilator therapy may improve outcomes.[77]

19 Cardiopulmonary Complications

Case 2: A 60-year-old female presented to the ED with sudden loss of consciousness and shortness of breath (intubated at the field for GCS 8 and hypoxia). Husband reports patient had been having headaches for 2 days prior to presentation. Upon arrival to the ED, patient remained comatose with GCS of 7T. Patient was also noted to have anisocoria with dilated and fixed right pupil and opthalmoplegia with right eye deviated down and out. Left pupil was noted to be mid-positioned with normal pupillary response. Initial

blood pressure was 155/86 mm hg. Non-contrast CT brain showed subarachnoid hemorrhage predominantly in the basal cisterns and right Sylvian fissure along with the presence of intraventricular hemorrhage and mild hydrocephalus. CT Angiogram revealed a right posterior communicating artery aneurysm. Chest X-Ray showed bilateral alveolar opacities. A point of care ultrasound in the ED showed normal cardiac function.

Cardiopulmonary alterations are common systemic complications after SAH and range from minor EKG changes to severe cardiomyopathy and acute respiratory distress syndrome (ARDS). Cardiac enzyme elevation and EKG changes are common after aSAH, especially with high grade aSAH and may have prognostic implications. Common EKG changes may include ST-T changes with peaked T- subhyaloidwave, T-wave inversion, ST-segment depression/elevation and QT prolongation. Arrhythmia including atrial fibrillation or flutter may occur in up to 4% of patients and have prognostic relevance. Furthermore, elevation of troponin may be noted in up to 30% of patients.

Although the exact mechanism of cardiac injury is not clear, it is thought to be a catecholamine-mediated injury. Neurogenic stunned myocardium is a form of reversible non-ischemic cardiomyopathy resulting from catecholamine excess. Female sex and poor clinical grade at presentation have been associated with the development of neurogenic

stunned myocardium. Although the term Takotsubo cardiomyopathy and neurogenic stunned myocardium are often used interchangeably in the clinical setting, some differences related to risk factors and clinical presentations have been noted. Regardless of the term used, cardiac dysfunction leading to left ventricular failure with impaired cardiac output, hypotension, and pulmonary edema may lead to severe hypoperfusion and hypoxia causing reduction in cerebral perfusion pressure and brain tissue oxygenation that can precipitate catastrophic secondary brain injury. Baseline cardiac assessment with serial EKGs, cardiac enzymes and echocardiography is hence recommended, especially in patients with evidence of myocardial dysfunction. Standard clinical management of heart failure is indicated, while recognizing the importance of maintaining cerebral perfusion pressure within normal limits.

Apart from pulmonary edema related to myocardial injury/stunned myocardium, neurogenic pulmonary edema (NPE) is known to occur in 8-29% of patients with aSAH with highest incidence in patients with rupture of posterior circulation aneurysms and is related with poor neurologic outcome. Although NPE can occur in delayed fashion with neurologic worsening, it is commonly present on presentation with initial brain injury as noted in case 2. NPE is defined as the increase in interstitial and alveolar lung fluid occurring as a direct consequence of acute brain injury. Patients present with clinical and radiological signs of acute pulmonary edema in the absence of cardiac dysfunction or other definite causes of acute lung injury or ARDS. Management of NPE or ARDS in patients with aSAH is focused in avoiding excess fluid intake and judicious use of diuretics while avoiding dehydration as volume contraction can precipitate secondary brain injury. Additionally, permissive hypercapnia routinely used in ARDS may worsen cerebral edema and should be avoided in these patients.

20 Nursing Considerations

Nursing care should include vigilant monitoring for signs and symptoms of hydrocephalus and aneurysmal rebleed including decreased level of consciousness, poorly reactive pupils, gaze abnormalities and other neurologic exam changes. If these neurologic changes are noted, the provider should be notified of changes and obtain a non-contrast head CT anticipated. If the head CT demonstrates hydrocephalus, an EVD may be placed at the bedside with the assistance of nursing. Alternatively, if the head CT demonstrates aneurysm rebleeding, preparations should be made for possible urgent surgical treatment and/or antifibrinolytic therapy.

Nursing considerations regarding the effects of nimodipine include risk of hypotension after administration. If hypotension is noted at a dose of 60 mg nimodipine every 4 hours by mouth, the dose can be changed to 30 mg of nimodipine every 2 hours.

There is little research on pain management for SAH. Headache after SAH is often severe and will likely require the use of multiple non-opioid and opioid medications. Pain should frequently be monitored and treated, with an effort to use non-opioid medications to preserve level of consciousness. If sedation is necessary, the least sedating agent should be used in order to preserve the assessment of the patient's neurologic status.

Clustering nursing care such as oral care, repositioning, endotracheal suctioning, and hygienic care has been associated with increases in ICP. In the presence of increased ICP or unsecured aneurysm, nursing care should be performed in intervals. The patient should remain on bedrest when the aneurysm is unsecured, with the head of bed (HOB) at least 30°. The patient should be NPO in the initial hours after SAH until a swallow screen is performed by the nurse or the speech language pathologist. If the patient fails the initial swallow screen the patient will remain strictly NPO until further evaluation by the speech language pathologist. Consider obtaining enteral access with a nasogastric tube if necessary.

Strict intake and output should be measured in patients who have had an SAH, with efforts to keep the patient euvolemic. Hypervolemia has been associated with higher rates of vasospasm and longer length of stay. Once the aneurysm is secured, best practices include early mobilization of the patient except if the patient is hemodynamically unstable or has intracranial hypertension.

21 Pediatric Considerations

In the pediatric population, the incidence of aSAH is lower compared to adults. Nonetheless, SAH represents the most common initial manifestation of cerebral aneurysms in children.[59,61,64,65] Because of different etiologies (traumatic, excessive hemodynamic stress, arteriopathies, infectious, inflammatory, cancer related, familial and idiopathic) location and morphology of pediatric aneurysms may differ from adults.[61–62] Aneurysms may occur spontaneously in such conditions as Ehlers-Danlos syndrome or Marfan syndrome, or also may occur with increased incidence within specific families or resulting from traumatic dissections.[59,63,64,65,68] The clinical symptoms suggestive of aSAH may be similar to adults, with common symptoms manifesting as sudden unexplained

headaches, emesis, seizures, focal neurologic deficits, or decreased level of consciousness. Children of young age may present with irritability as they are not able to express concerns for new onset headaches or nausea, so careful clinical history-taking from parents or guardians is needed.

For aSAH, neuroimaging with head CT remains the primary radiographic modality for evaluation.[69] Use of CTA or MRA can be helpful in localizing cerebral aneurysms.[62,68] In patients without obvious SAH on imaging but strong clinical suspicion, lumbar puncture may be used to confirm the diagnosis. Because of the wide differential of potential etiologies to consider in children with SAH, in suspicious clinical context, initial investigation should entail an evaluation for possible abusive head trauma including skeletal surveys and retinal examinations for signs towards such a diagnosis.[67] Once the diagnosis of aSAH is established, standard four-vessel angiography should be performed.[70,71]

Initial management for children with aSAH is to focus on stabilization and prevention of secondary complications, such as re-bleeding. EVD placement may be indicated and should be placed and managed with the same caution for re-rupture as in adults.

Strict attention towards establishment of normal volume status is needed to mitigate the risk of cerebrovascular vasospasm. Adequate analgesia and sedation should be balanced with the need to obtain appropriate neurologic examinations. Allowing parents to remain at their bedside may aid in alleviating the anxiety of young children. Antihypertensive medications such as nicardipine may be necessary prior to definitive treatment of unruptured aneurysms, with rebleeding being the most serious early complication.[66] In children, BP management needs to be age- and patient-specific, balancing the risk of cerebral hypoperfusion (either due to intracranial hypertension or cerebral vasospasms/DCI) and rebleeding. The use of nimodipine has not been well studied in the pediatric population but given the available evidence in adults, may warrant usage if hemodynamically tolerated. A dose of 1 mg/kg of nimodipine administered every 4 hours has been used in pediatric patient populations.[78]

Management preventing and treating cerebrovascular vasospasm remains important for children. Both cerebrovascular vasospasms and DCI have lower incidence in children as compared to adults, but these findings may reflect decreased monitoring in children. Normative values for TCD mean flow velocities are now available in children and trending these values early may help screen for cerebrovascular vasospasm.[73]

Because of the rare incidence of aSAH in children, treatment should ideally occur at high-volume centers with availability of experienced treatment teams including pediatric neurosurgeons, interventional neuroradiologists, and neurocritical care specialists. Care may often require a multidisciplinary team of adult and pediatric providers to facilitate appropriate endovascular or neurosurgical procedures for definitive management of complex aneurysms.

Clinical Pearls
Presentation is often “the worst headache of life”
Noncontrast head CT is highly sensitive if done within the first few days of symptom onset
LP should be done if CT is negative, and the history is suggestive of aSAH; CSF with xanthochromia and elevated RBCs is pathognomonic
CTA is helpful for detection of bleeding sources; Digital subtraction angiography is gold standard
Monitor for and decrease the risk of rebleeding prior to securing aneurysm: control BP, correct coagulopathies, minimize overstimulation
Treat hydrocephalus
Secure aneurysm within 24 hours
Initiate enteral nimodipine for the prevention of delayed cerebral ischemia and monitor for vasospasm
Cardiorespiratory complications may be present

22 Starred References

**Landmark paper

* Important paper

*1 (Diringer MN, et al.): Discussion of the complex critical care issues involved in the care of patients with subarachnoid hemorrhage.

*2 (Connolly ES, et al): Comprehensive recommendations on the management of aneurysmal subarachnoid hemorrhage.

**37 (Molyneux A, et al.): Comparison of endovascular detachable-coil treatment or craniotomy and clipping in the treatment of aneurysmal subarachnoid hemorrhage.

**38 (Phillips TJ, et al.): Timing of treatment of aneurysmal subarachnoid hemorrhage and its effect on clinical outcome.

**53 (Allen GS, et al.): Effect of treatment with calcium channel blockers in patients presenting with aneurysmal subarachnoid hemorrhage to reduce the occurrence of severe neurologic deficits due to cerebral arterial spasm.

23 References

1. * Diringer MN, Bleck TP, Claude Hemphill J, 3rd, et al., Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society’s Multidisciplinary Consensus Conference. Neurocrit Care, 2011; 15: 211-40. (Discussion of the complex critical care issues involved in the care of patients with subarachnoid hemorrhage)

2. * Connolly ES, Jr., Rabinstein AA, Carhuapoma JR, et al., Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke, 2012; 43: 1711-37. (Comprehensive recommendations on the management of aneurysmal subarachnoid hemorrhage)

3. Edlow JA, Malek AM, and Ogilvy CS, Aneurysmal subarachnoid hemorrhage: update for emergency physicians. J Emerg Med, 2008; 34: 237-51.

4. Linn FH and Wijdicks EF, Causes and management of thunderclap headache: a comprehensive review. Neurologist, 2002; 8: 279-89.
5. Schievink WI, Karemaker JM, Hageman LM, et al., Circumstances surrounding aneurysmal subarachnoid hemorrhage. Surg Neurol, 1989; 32: 266-72.
6. Suarez JI, Tarr RW, and Selman WR, Aneurysmal subarachnoid hemorrhage. N Engl J Med, 2006; 354: 387-96.
7. Pope JV and Edlow JA, Favorable response to analgesics does not predict a benign etiology of headache. Headache, 2008; 48: 944-50.
8. Edlow JA, Panagos PD, Godwin SA, et al., Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with acute headache. Ann Emerg Med, 2008; 52: 407-36.
9. Vermeulen MJ and Schull MJ, Missed diagnosis of subarachnoid hemorrhage in the emergency department. Stroke, 2007; 38: 1216-21.
10. Edlow JA and Caplan LR, Avoiding pitfalls in the diagnosis of subarachnoid hemorrhage. N Engl J Med, 2000; 342: 29-36.
11. Kowalski RG, Claassen J, Kreiter KT, et al., Initial misdiagnosis and outcome after subarachnoid hemorrhage. JAMA, 2004; 291: 866-9.
12. Perry JJ, Stiell IG, Sivilotti ML, et al., High risk clinical characteristics for subarachnoid haemorrhage in patients with acute headache: prospective cohort study. BMJ, 2010; 341: c5204.
13. Jauch EC, Cucchiara B, Adeoye O, et al., Part 11: adult stroke: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardio- vascular Care. Circulation, 2010; 122: S818-28.
14. Advanced Cardiac Life Support. 2019; Available from: https://acls.com/free-resources/knowledge-base/stroke/tools-used-for-neurological-examination-in-stroke Accessed July 15, 2019.
15. Bardach NS, Zhao S, Gress DR, et al., Association between subarachnoid hemorrhage outcomes and number of cases treated at California hospitals. Stroke, 2002; 33: 1851-6.
16. Berman MF, Solomon RA, Mayer SA, et al., Impact of hospital-related factors on outcome after treatment of cerebral aneurysms. Stroke, 2003; 34: 2200-7.
17. Joint Commission for Comprehensive Stroke. Specifications Manual for Joint Commission National Quality Measures (v2018A). 2018 [cited 2019 1/14/19]; Available from: https://manual.jointcommission.org/releases/TJC2018A/ComprehensiveStroke.html.
18. Det Norske Veritas (DNV). Stroke Care Certification Programs. 2019 [cited 2019 February 21, 2019]; Available from: https://www.dnvgl.us/assurance/healthcare/stroke-c erts.html.
19. Cuvinciuc V, Viguier A, Calviere L, et al., Isolated acute nontraumatic cortical subarachnoid hemorrhage. AJNR Am J Neuroradiol, 2010; 31: 1355-62.
20. Kumar S, Goddeau RP, Jr., Selim MH, et al., Atraumatic convexal subarachnoid hemorrhage: clinical presentation, imaging patterns, and etiologies. Neurology, 2010; 74: 893-9.
21. Byyny RL, Mower WR, Shum N, et al., Sensitivity of noncontrast cranial computed tomography for the emergency department diagnosis of subarachnoid hemorrhage. Ann Emerg Med, 2008; 51: 697-703.
22. Perry JJ, Stiell IG, Sivilotti ML, et al., Sensitivity of computed tomography performed within six hours of onset of headache for diagnosis of subarachnoid haemorrhage: prospective cohort study. BMJ, 2011; 343: d4277.
23. Vermeulen M, Hasan D, Blijenberg BG, et al., Xanthochromia after subarachnoid haemorrhage needs no revisitation. J Neurol Neurosurg Psychiatry, 1989; 52: 826-8.
24. Perry JJ, Sivilotti ML, Stiell IG, et al., Should spectrophotometry be used to identify xanthochromia in the cerebrospinal fluid of alert patients suspected of having subarachnoid hemorrhage? Stroke, 2006; 37: 2467-72.

25. Edlow JA, Bruner KS, and Horowitz GL, Xanthochromia. Arch Pathol Lab Med, 2002; 126: 413-5.
26. Linn FH, Voorbij HA, Rinkel GJ, et al., Visual inspection versus spectrophotome- try in detecting bilirubin in cerebrospinal fluid. J Neurol Neurosurg Psychiatry, 2005; 76: 1452-4.
27. Shah KH and Edlow JA, Distinguishing traumatic lumbar puncture from true subarachnoid hemorrhage. J Emerg Med, 2002; 23: 67-74.
28. Perry JJ, Alyahya B, Sivilotti ML, et al., Differentiation between traumatic tap and aneurysmal subarachnoid hemorrhage: prospective cohort study. BMJ, 2015; 350: h568.
29. Chalela JA, Kidwell CS, Nentwich LM, et al., Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison. Lancet, 2007; 369: 293-8.
30. Kidwell CS, Chalela JA, Saver JL, et al., Comparison of MRI and CT for detection of acute intracerebral hemorrhage. JAMA, 2004; 292: 1823-30.
31. Mitchell P, Wilkinson ID, Hoggard N, et al., Detection of subarachnoid haem- orrhage with magnetic resonance imaging. J Neurol Neurosurg Psychiatry, 2001; 70: 205-11.
32. Sohn CH, Baik SK, Lee HJ, et al., MR imaging of hyperacute subarachnoid and intraventricular hemorrhage at 3T: a preliminary report of gradient echo T2*-weighted sequences. AJNR Am J Neuroradiol, 2005; 26: 662-5.
33. Carstairs SD, Tanen DA, Duncan TD, et al., Computed tomographic angiography for the evaluation of aneurysmal subarachnoid hemorrhage. Acad Emerg Med, 2006; 13: 486-92.
34. McCormack RF and Hutson A, Can computed tomography angiography of the brain replace lumbar puncture in the evaluation of acute-onset headache after a negative noncontrast cranial computed tomography scan? Acad Emerg Med, 2010; 17: 444-51.
35. Probst MA and Hoffman JR, Computed Tomography Angiography of the Head Is a Reasonable Next Test After a Negative Noncontrast Head Computed Tomography Re- sult in the Emergency Department Evaluation of Subarachnoid Hemorrhage. Ann Emerg Med, 2016; 67: 773-774.
36. Edlow JA, What are the unintended consequences of changing the diagnostic paradigm for subarachnoid hemorrhage after brain computed tomography to computed tomographic angiography in place of lumbar puncture? Acad Emerg Med, 2010; 17: 991-5; discussion 996-7.
37. **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: 1267-74. (Comparison of endovascular detachable-coil treatment or craniotomy and clipping in the treat- ment of aneurysmal subarachnoid hemorrhage).
38. * Phillips TJ, Dowling RJ, Yan B, et al., Does treatment of ruptured intracranial aneurysms within 24 hours improve clinical outcome? Stroke, 2011; 42: 1936-45. (Timing of treatment of aneurysmal subarachnoid hemorrhage and its effect on clinical outcome)
39. Pandey AS, Gemmete JJ, Wilson TJ, et al., High Subarachnoid Hemorrhage Patient Volume Associated With Lower Mortality and Better Outcomes. Neurosurgery, 2015; 77: 462-70.
40. 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.
41. Hunt WE and Hess RM, Surgical risk as related to time of intervention in the repair of intracranial aneurysms. J Neurosurg, 1968; 28: 14-20.
42. Report of World Federation of Neurological Surgeons Committee on a Universal Subarachnoid Hemorrhage Grading Scale. J Neurosurg, 1988; 68: 985-6.
43. Frontera JA, Claassen J, Schmidt JM, et al., Prediction of symptomatic

vasospasm after subarachnoid hemorrhage: the modified fisher scale. Neurosurgery, 2006; 59: 21-7; discussion 21-7.
44. Rhoney DH, Tipps LB, Murry KR, et al., Anticonvulsant prophylaxis and timing of seizures after aneurysmal subarachnoid hemorrhage. Neurology, 2000; 55: 258-65.
45. Jaja BNR, Schweizer TA, Claassen J, et al., The SAFARI Score to Assess the Risk of Convulsive Seizure During Admission for Aneurysmal Subarachnoid Hemorrhage. Neurosurgery, 2018; 82: 887-893.
46. Naidech AM, Kreiter KT, Janjua N, et al., Phenytoin exposure is associated with functional and cognitive disability after subarachnoid hemorrhage. Stroke, 2005; 36: 583- 7.
47. Frontera JA, Lewin JJ, 3rd, Rabinstein AA, et al., Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage: A Statement for Healthcare Professionals from the Neurocritical Care Society and Society of Critical Care Medicine. Neurocrit Care, 2016; 24: 6-46.
48. Ghani GA, Sung YF, Weinstein MS, et al., Effects of intravenous nitroglycerin on the intracranial pressure and volume pressure response. J Neurosurg, 1983; 58: 562-5.
49. van Gijn J, Hijdra A, Wijdicks EF, et al., Acute hydrocephalus after aneurysmal subarachnoid hemorrhage. J Neurosurg, 1985; 63: 355-62.
50. Graff-Radford NR, Torner J, Adams HP, Jr., et al., Factors associated with hydro- cephalus after subarachnoid hemorrhage. A report of the Cooperative Aneurysm Study. Arch Neurol, 1989; 46: 744-52.
51. Hillman J, Fridriksson S, Nilsson O, et al., Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurysmal subarachnoid hem- orrhage: a prospective randomized study. J Neurosurg, 2002; 97: 771-8.
52. Schuette AJ, Hui FK, Obuchowski NA, et al., An examination of aneurysm rerup- ture rates with epsilon aminocaproic acid. Neurocrit Care, 2013; 19: 48-55.
53. ** Allen GS, Ahn HS, Preziosi TJ, et al., Cerebral arterial spasm–a controlled trial of nimodipine in patients with subarachnoid hemorrhage. N Engl J Med, 1983; 308: 619-24. (Effect of treatment with calcium channel blockers in patients presenting with aneurysmal subarachnoid hemorrhage to reduce the occurrence of severe neurologic deficits due to cerebral arterial spasm)
54. Pickard JD, Murray GD, Illingworth R, et al., Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. BMJ, 1989; 298: 636-42.
55. Dorhout Mees SM, Rinkel GJ, Feigin VL, et al., Calcium antagonists for aneurys- mal subarachnoid haemorrhage. Cochrane Database Syst Rev, 2007: CD000277.
56. Kronvall E, Undren P, Romner B, et al., Nimodipine in aneurysmal subarachnoid hemorrhage: a randomized study of intravenous or peroral administration. J Neurosurg, 2009; 110: 58-63.
57. Engelborghs S, Niemantsverdriet E, Struyfs H, et al., Consensus guidelines for lumbar puncture in patients with neurological diseases. Alzheimers Dement (Amst), 2017; 8: 111-126.
58. Fung C, Mavrakis E, Filis A, Fischer I, Suresh M, Tortora A, Cornelius JF, Bostel- mann R, Gralla J, Beck J, Raabe A, Khan MO, Steiger HJ, Petridis AK. Anatomical evalu- ation of intracranial aneurysm rupture risk in patients with multiple aneurysms. Neurosurg Rev. 2019 Jun;42(2):539-547.
59. Shinkawa T, Ramakrishnaiah RH, Eble BK. Subarachnoid haemorrhage from undiagnosed mycotic aortic aneurysm in a child. Cardiol Young. 2018 Mar;28(3):461-463.
60. Skoch J, Tahir R, Abruzzo T, Taylor JM, Zuccarello M, Vadivelu S. Predicting symptomatic cerebral vasospasm after aneurysmal subarachnoid hemorrhage with an arti- ficial neural network in a pediatric population. Childs Nerv Syst. 2017 Dec;33(12):2153- 2157.

61. Deora H, Rao KVLN, Somanna S, Srinivas D, Shukla DP, Bhat DI. Surgically Managed Pediatric Intracranial Aneurysms: How Different Are They from Adult Intracra- nial Aneurysms? Pediatr Neurosurg. 2017;52(5):313-317.
62. Aeron G, Abruzzo TA, Jones BV. Clinical and imaging features of intracranial arterial aneurysms in the pediatric population. Radiographics. 2012 May-Jun;32(3):667-81
63. Burke MJ. Occult aneurysmal hemorrhage in a child. Case report and literature review. Pediatr Neurosurg. 2000 Nov;33(5):274-277.
64. Manz HJ, Vester J, Lavenstein B. Dissecting aneurysm of cerebral arteries in childhood and adolescence. Case report and literature review of 20 cases. Virchows Arch A Pathol Anat Histol. 1979 Oct;384(3):325-35.
65. Manz HJ, Vester J, Lavenstein B. Dissecting aneurysm of cerebral arteries in childhood and adolescence. Case report and literature review of 20 cases. Virchows Arch A Pathol Anat Histol. 1979 Oct;384(3):325-35.
66. Beez T, Steiger HJ, Hänggi D. Evolution of Management of Intracranial Aneurysms in Children: A Systematic Review of the Modern Literature. J Child Neurol. 2016 May;31(6):773-83.
67. Orman G, Kralik SF, Meoded A, Desai N, Risen S, Guisman TAGM. MRI Findings in Pediatric Abusive Head Trauma: A Review. J Neuroimaging. 2020 Jan; 30(1):15- 27.
68. Penn DL, Lanpher AB, Klein JM, Kozakewich HPW, Kahle KT, Smith ER, Orbach DB. Multimodal treatment approach in a patient with multiple intracranial myxoma- tous aneurysms. J Neurosurg Pediatr. 2018 Mar;21(3):315-321.
69. Ghali MGZ, Srinivasan VM, Cherian J, Kim L, Siddiqui A, Aziz-Sultan MA, Froehler M, Wakhloo A, Sauvageau E, Rai A, Chen SR, Johnson J, Lam SK, Kan P. Pediatric Intracranial Aneurysms: Considerations and Recommendations for Follow-Up Imaging. World Neurosurg. 2018 Jan;109:418-431.
70. Sullivan S, Aguilar-Salinas P, Santos R, Beier AD, Hanel RA. Three-dimensional printing and neuroendovascular simulation for the treatment of a pediatric intracranial aneurysm: case report. J Neurosurg Pediatr. 2018 Dec 01;22(6):672-677.
71. Colby GP, Jiang B, Bender MT, Beaty NB, Westbroek EM, Xu R, Lin LM, Cam- pos JK, Tamargo RJ, Huang J, Cohen AR, Coon AL. Pipeline-assisted coil embolization of a large middle cerebral artery pseudoaneurysm in a 9-month-old infant: experience from the youngest flow diversion case. J Neurosurg Pediatr. 2018 Nov 01;22(5):532-540.
72. Patro SN, Iancu D, Al Mansoori T, Lesiuk H, Vassilyadi M. Endovascular glue embolization of a radiation-induced lenticulostriate artery pseudoaneurysm in a pediatric patient with optic pathway glioma: Case report and review of literature. Interv Neurora- diol. 2018 Oct;24(5):499-508.
73. O'Brien NF. Reference values for cerebral blood flow velocities in critically, ill sedated children. Childs Nerv Syst. 2015 Dec;31(12):2269-76.
74. Perry JJ, Sivilotti MLA, Sutherland J, Hohl CM, Émond M, Calder LA, Vaillancourt C, Thirganasambandamoorthy V, Lesiuk H, Wells GA, Stiell IG. Validation of the Ottawa Subarachnoid Hemorrhage Rule in patients with acute headache. CMAJ. 2017 Nov 13;189(45):E1379-E1385. doi: 10.1503/cmaj.170072. Erratum in: CMAJ. 2018 Feb 12;190(6):E173. PMID: 29133539; PMCID: PMC5687926.
75. Kumar G, Dumitrascu OM, Chiang CC, O'Carroll CB, Alexandrov AV. Prediction of Delayed Cerebral Ischemia with Cerebral Angiography: A Meta-Analysis. Neurocrit Care. 2019 Feb;30(1):62-71.
76. Castle-Kirszbaum M, Lai L, Maingard J, Asadi H, Danks RA, Goldschlager T, Chandra RV. Intravenous milrinone for treatment of delayed cerebral ischaemia following subarachnoid haemorrhage: a pooled systematic review. Neurosurg Rev. 2021 Mar 8. doi: 10.1007/s10143-021-01509-1. Epub ahead of print. PMID: 33682040.
77. Jabbarli R, Pierscianek D, Rölz R, Darkwah Oppong M, Kaier K, Shah M, Taschner C, Mönninghoff C, Urbach H, Beck J, Sure U, Forsting M. Endovascular

treat- ment of cerebral vasospasm after subarachnoid hemorrhage: More is more. Neurology. 2019 Jul 30;93(5):e458-e466.
78. Heffren J, McIntosh AM, Reiter PD. Nimodipine for the prevention of cere- bral vasospasm after subarachnoid hemorrhage in 12 children. Pediatr Neurol. 2015 Mar;52(3):356-60. doi: 10.1016/j.pediatrneurol.2014.11.003. Epub 2014 Nov 11. PMID: 25585913.
79. Clinical Decision Rules to Rule Out Subarachnoid Hemorrhage for Acute Headache Jeffrey J. Perry, MD, MSc1; Ian G. Stiell, MD, MSc1; Marco L. A. Sivilotti, MD, MSc5,6; et al JAMA 2013;310(12):1248-1255

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