Etiology, clinical manifestations, and diagnosis of aneurysmal subarachnoid hemorrhage

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INTRODUCTION — Twenty percent of strokes are hemorrhagic, with subarachnoid hemorrhage (SAH) and intracerebral hemorrhage each accounting for 10 percent. The epidemiology, etiology, clinical manifestations, and diagnosis of aneurysmal SAH are reviewed here. The treatment of this disorder and the epidemiology and pathogenesis of intracranial aneurysms and management of unruptured aneurysms are discussed separately. Mycotic aneurysms and nonaneurysmal subarachnoid hemorrhage are also discussed separately. (See "Treatment of aneurysmal subarachnoid hemorrhage" and "Unruptured intracranial aneurysms" and "Overview of infected (mycotic) arterial aneurysm" and "Nonaneurysmal subarachnoid hemorrhage" and "Perimesencephalic nonaneurysmal subarachnoid hemorrhage".)

EPIDEMIOLOGY — Most SAHs are caused by ruptured saccular aneurysms. Other causes include trauma, arteriovenous malformations/fistulae, vasculitides, intracranial arterial dissections, amyloid angiopathy, bleeding diatheses, and illicit drug use (especially cocaine and amphetamines).

The prevalence of intracranial saccular aneurysms by radiographic and autopsy series is 5 percent, or 10 to 15 million people in the United States. Approximately 20 to 30 percent of patients have multiple aneurysms [1]. Aneurysmal SAH occurs at an estimated rate of 3 to 25 per 100,000 population [2,3]. The mean age at onset is 55 years [4]. In North America, this translates into approximately 30,000 affected persons per year. Thus, most aneurysms do not rupture. The risk of rupture of intracranial aneurysms is related in part to aneurysm size and is discussed separately. (See "Unruptured intracranial aneurysms", section on 'Natural history of unruptured aneurysms'.)

Most aneurysmal SAH occur between 40 and 60 years of age; however young children and the elderly can be affected [5,6]. African Americans appear to be at higher risk than Caucasian Americans [7]. There is a slightly higher incidence of aneurysmal SAH in women, which may relate to hormonal status (see 'Estrogen deficiency' below) [5,8].

RISK FACTORS — Most SAHs are due to the rupture of intracranial aneurysms. Because of this, risk factors for aneurysm formation overlap with risk factors for SAH. Risk factors that are primarily associated with formation of intracranial aneurysms are discussed separately. (See "Unruptured intracranial aneurysms".)

Stressful life events have not been convincingly shown to be a risk factor for SAH [9,10].
**Cigarette smoking** — Cigarette smoking appears to be the most important preventable risk factor for SAH [11-15]. The importance of cigarette smoking is illustrated by the following reports:

- A case-control study of 432 adults with SAH found that current cigarette smokers had a significantly increased risk of SAH compared with nonsmokers not exposed to secondhand smoke (odds ratio 5.0) [12]. Current and lifetime exposures showed a clear dose-dependent effect, and the risks appeared to be more prominent in women and in aneurysmal SAH. The risk attributable to cigarette smoking declined rapidly and largely disappeared within a few years of quitting. There was no significant effect of secondhand smoke.

- In a systematic review of 14 longitudinal and 23 case-control studies that included 3936 patients with SAH, current smoking was a significant risk factor for SAH in both the longitudinal (relative risk [RR] 2.2, 95% CI 1.3-3.6) and case-control studies (odds ratio [OR] 3.1, 95% CI 2.7-3.5) [13].

- An analysis of data from the Asia Pacific Cohort Studies Collaboration (APCSC) involving 26 cohorts with 306,620 participants and 236 SAH events found that the risk for SAH was significantly associated with current smoking (hazard ratio [HR] 2.4, 95% CI 1.8-3.4) [14].

**Hypertension** — Hypertension is a major risk factor for SAH [11,13-17]. The best data come from the systematic review cited above that included 3936 patients with SAH [13]. Hypertension was significantly associated with SAH risk in both the longitudinal (RR 2.5, 95% CI 2.0-3.1) and case-control studies (OR 2.6, 95% CI 2.0-3.1).

**Alcohol** — Moderate to heavy alcohol consumption appears to increase the risk of SAH (figure 1) [13,18]. In the systematic review cited above, excessive alcohol intake was a significant risk factor for SAH in both the longitudinal (RR 2.1, 95% CI 1.5-2.8) and case-control studies (OR 1.5, 95% CI 1.3-1.8) [13].

**Genetic risk** — Most aneurysmal SAHs are of nongenetic origin [19]. However, a number of relatively rare inherited conditions are associated with increased risk of cerebral aneurysm and SAH. These include autosomal dominant polycystic kidney disease, glucocorticoid-remediable aldosteronism, and Ehler Danlos syndrome. The risk of aneurysmal SAH associated with these conditions is discussed separately. (See "Screening for intracranial aneurysm", section on 'Hereditary syndromes associated with aneurysm formation'.)

A family history of SAH also increases the risk of SAH in individuals without one of these conditions. As an example, one case-control study found that patients with a family history of SAH had an odds ratio of 4.0 (95% CI 2.0-8.0) for SAH compared with controls [20]. Similarly, another study found that first-degree relatives of patients with SAH have a three to five-fold increased risk of SAH compared with the general population [21]. It may be reasonable to screen some family members for the presence of cerebral aneurysm. This issue is discussed in detail separately. (See "Screening for intracranial aneurysm", section on 'Relatives of patients with cerebral aneurysm'.)

The genetic susceptibility to SAH appears to be heterogeneous. Some familial SAH pedigrees are most consistent with autosomal dominant inheritance, while others are more consistent with autosomal recessive or multifactorial transmission [22,23]. One study found evidence of anticipation in two successive generations of familial SAH, with affected parents significantly older than affected children (55.2 versus 35.4 years, respectively) [24]. Some evidence points to the elastin gene on chromosome 7q as a
candidate gene related to the development of familial [25,26] and sporadic [27] SAH. Other evidence supports linkage of familial SAH to chromosomes 1p [28], 2p [29], 9p [30], 11q, 14q [31], 19q [32-34], and Xp22 [32,34]. A polymorphism affecting the platelet adhesive glycoprotein GPIIIa HPA-1 (HPA comes from human platelet alloantigen; GPIIIa HPA-1 is also called PIA) is associated with increased risk of thrombosis and a decreased risk of SAH (odds ratio 0.48; 95% CI 0.24-0.96) [35].

Familial susceptibility to SAH may be nongenetic and attributed to environmental and other shared risk factors [19].

**Sympathomimetic drugs** — In case-control studies, phenylpropanolamine in appetite suppressants, and possibly cold remedies, appeared to be an independent risk factor for hemorrhagic stroke (including intracerebral hemorrhage and subarachnoid hemorrhage) in women [36,37].

Cocaine abuse has been associated with both aneurysmal and nonaneurysmal SAH [38-40]. (See "Nonaneurysmal subarachnoid hemorrhage", section on 'Other causes'.)

**Estrogen deficiency** — There is a female preponderance for aneurysms ranging from 54 to 61 percent [8]. In one case-control study, premenopausal women without a history of smoking or hypertension were at reduced risk of SAH compared with age-matched postmenopausal women (odds ratio 0.24) [41]. Furthermore, the use of estrogen replacement therapy was associated with a reduced risk of SAH in postmenopausal women (odds ratio 0.47). Risk reduction with the use of estrogen replacement therapy has been seen in other studies as well [13,42].

Hormonal effects may also explain the association between risk of SAH and repeated childbirth that was observed in one case-control study; each additional parity increased the risk with an OR = 1.34 [43]. However, physical and environmental factors during pregnancy and delivery are also likely factors.

**Antithrombotic therapy** — Sufficient data are not available to determine whether anticoagulant (eg, warfarin) or antiplatelet therapy increase the risk of aneurysm rupture [44]. However, anticoagulation therapy does appear to increase the severity of a SAH. (See "Anticoagulant and antiplatelet therapy in patients with an unruptured intracranial aneurysm".)

**Statins** — The relationship between cholesterol status, statin use, and the risk of ischemic versus hemorrhagic cerebrovascular events is complex. Statin use is associated with an overall lower risk of total and ischemic cerebrovascular events, but there is some concern that low cholesterol levels and statin use may increase the risk of intracerebral hemorrhage. (See "Secondary prevention of stroke: Risk factor reduction").

One case control study found that current statin use was not significantly associated with a lower SAH risk, and that recent statin drug withdrawal increased the risk of SAH [45]. However, the effect of statin withdrawal was highest in patients who had also stopped taking antihypertensive drugs.

**CLINICAL MANIFESTATIONS** — Rupture of an aneurysm releases blood directly into the cerebrospinal fluid (CSF) under arterial pressure. The blood spreads quickly within the CSF, rapidly increasing intracranial pressure. The bleeding usually lasts only a few seconds, but rebleeding is common and occurs more often within the first day.

Consistent with the rapid spread of blood, the symptoms of SAH typically begin abruptly, occurring at night in 30 percent of cases. The premier symptom is a sudden, severe headache (97 percent of cases) classically described as the "worst headache of my life." The headache is lateralized in 30 percent of patients, predominantly to the side of the
aneurysm. The onset of the headache may or may not be associated with a brief loss of consciousness, seizure, nausea or vomiting, and meningismus (figure 2) [46]. In one series, these occurred in 53, 77, and 35 percent respectively [47]. Meningismus and often lower back pain may not develop until several hours after the bleed since it is caused by the breakdown of blood products within the CSF, which lead to an aseptic meningitis [48].

Approximately 30 to 50 percent of patients have a minor hemorrhage or "warning leak," manifested only by a sudden and severe headache (the sentinel headache) that precedes a major SAH by 6 to 20 days [46]. A systematic literature review through September 2002 found that the incidence of sentinel headaches in aneurysmal SAH ranged from 10 to 43 percent [49].

The complaint of the sudden onset of severe headache is sufficiently characteristic that a minor SAH should always be considered. In a prospective study of 148 patients presenting with sudden and severe headache, for example, SAH was present in 25 percent overall and in 12 percent of those in whom headache was the only symptom [50]. Similar findings were noted in another report in which 20 of 107 patients with the "worst headache of my life" had an SAH [51].

Physical exertion may be an acute trigger for SAH. A case-crossover study in 338 patients with SAH found that patients were more likely to have engaged in moderate or greater exertion in the two hours prior to SAH than in the same two-hour period on the previous day (odds ratio 2.7, 95% CI 1.6-4.6) [52]. Acute elevation in blood pressure is believed to be the mechanism by which physical exertion acts as a trigger for SAH and may also play a role in the observed associations between caffeine consumption, acute anger or startling, and sexual exertion as triggers for SAH [53]. A trigger event preceding SAH is not invariable [40].

COMPLICATIONS—Subarachnoid hemorrhage (SAH) is associated with a high mortality rate [54]. A systematic review found that the average case fatality rate for SAH was 51 percent [55]. Approximately 10 percent of patients with aneurysmal SAH die prior to reaching the hospital, 25 percent die within 24 hours of SAH onset, and about 45 percent die within 30 days [56].

Mortality rates due to SAH appear to be decreasing over time in Western populations [57-59]. Improvements in rates of smoking, treatment of hypertension, and management of SAH are plausible but unproven reasons for the reduction in mortality. Improved diagnostic accuracy over time, including exclusion of SAH mimics, may also be playing a role.

A number of additional complications commonly occur in patients who have suffered a SAH:

- Rebleeding
- Vasospasm and delayed cerebral ischemia
- Hydrocephalus
- Increased intracranial pressure
- Seizures
- Hyponatremia
- Cardiac abnormalities
- Hypothalamic dysfunction and pituitary insufficiency [60]

Rebleeding — Most studies have found that the risk of rebleeding is highest in the first 24 hours after SAH [61-63], particularly within six hours of the initial hemorrhage [62]. The risk of rebleeding in the first 24 hours ranges from 2.6 to 4 percent [61,63]. Most
Rebleeding (73 percent) occurs within the first 72 hours of ictus [63]. Factors that may be independent predictors of rebleeding include:

- the Hunt-Hess grade on admission [62,63]
- maximal aneurysm diameter [63]
- a higher initial blood pressure [40]
- a sentinel headache preceding SAH [64]
- a longer interval from ictus to admission [40]
- early ventriculostomy (prior to aneurysm treatment) [40]

The overall incidence of rebleeding after initial SAH in the modern era is uncertain. A prospective study from a tertiary care center involving 574 hospitalized patients admitted within 14 days of SAH found a rebleeding rate of 6.9 percent by three months [63]. This rate may have been biased by over representation of high-risk aneurysms (eg, large, anatomically complex, or located in the posterior circulation).

Rebleeding is usually diagnosed on the basis of an acute deterioration of neurologic status accompanied by appearance of new hemorrhage on head CT scan. Lumbar puncture is harder to evaluate because xanthochromia can persist for two weeks or more. (See 'Lumbar puncture' below.)

Only aneurysm treatment is effective for the prevention of rebleeding. (See "Treatment of aneurysmal subarachnoid hemorrhage", section on 'Treatment of aneurysms'.)

The prognosis of rebleeding after SAH is discussed separately. (See "Treatment of aneurysmal subarachnoid hemorrhage", section on 'Management of complications'.)

**Vasospasm** — Vasospasm causes symptomatic ischemia and infarction in approximately 20 to 30 percent of patients with aneurysmal SAH; it is the leading cause of death and disability after aneurysm rupture [65,66]. Vasospasm typically begins no earlier than day three after hemorrhage, reaching a peak at days seven to eight. The onset of clinical vasospasm is characterized by a decline in neurologic status, including the onset of focal neurologic abnormalities. The severity of symptoms depends upon the artery affected and the degree of collateral circulation.

Transcranial Doppler (TCD) sonography is useful for detecting and monitoring vasospasm in spontaneous SAH, and it is probably useful for detecting vasospasm after traumatic SAH [67,68]. Velocity changes detected by TCD typically precede the clinical sequelae of vasospasm. Daily recordings offer a window of opportunity to treat patients prior to clinical decline. (See "Treatment of aneurysmal subarachnoid hemorrhage".)

Preliminary but accumulating data suggest that brain perfusion asymmetry demonstrated on CT perfusion (CTP) scanning in the acute stage of SAH may be a useful and highly sensitive method for predicting delayed cerebral ischemia, which is most cases, is presumably due to vasospasm [69-71]. A finding of perfusion-diffusion mismatch on MRI may be another method of detecting brain areas at risk of infarction in this setting [72]. However, the clinical utility of either of these methods remains to be established.

**Pathogenesis** — The pathogenesis of delayed cerebral vasospasm involves an interaction between the metabolites of blood and the vasculature. Spasmodogenic substances generated during the lysis of subarachnoid blood clots can cause endothelial damage and smooth muscle contraction [73]. The vascular endothelium produces nitric oxide, which tonically dilates the cerebral vasculature; endothelial damage may interfere with nitric oxide production, leading to vasoconstriction and an impaired response to vasodilators [74]. In addition, increased release of the potent vasoconstrictor endothelin may play a major role in the induction of cerebral vasospasm after SAH [73].
**Risk factors** — The location of blood on computed tomography (CT) scan and its extent can help predict the likelihood of complicating cerebral vasospasm [75-77]. In one series, severe vasospasm was correctly predicted and localized in 20 of 22 patients using the CT criteria of clots larger than 3 x 5 mm or layers of blood more than 1 mm thick [76]. Radiologic grading scales including those of Fisher (table 1) and Claassen (table 2) are often used to predict the likelihood of vasospasm and cerebral ischemia. (See "Subarachnoid hemorrhage grading scales").

Other factors that may increase the risk of vasospasm include age less than 50 years and hyperglycemia [78,79]. Most [80-82] but not all [78] studies have found that poor clinical grade (eg, Hunt-Hess grade 4 or 5, or Glasgow Coma Scale score <14) is associated with an increased risk of vasospasm, and a longer duration of unconsciousness after SAH may also be a predictor [80]. In contrast, the type of therapy chosen (surgical versus endovascular) does not appear to influence risk.

Evidence from a retrospective cohort study examining vasoactive medication usage at the time of SAH suggests that patients exposed to statins and selective serotonin reuptake inhibitors (SSRIs) have a higher risk for vasospasm [82]. In addition, SSRI users may have a higher risk for symptomatic vasospasm with focal neurologic worsening.

The increased risk of vasospasm with statin use may be related to rebound effects from statin discontinuation at the time of SAH, as there is some evidence that statins may be useful for the prevention of vasospasm after SAH. This issue is discussed separately. (See "Treatment of aneurysmal subarachnoid hemorrhage", section on 'Prevention of vasospasm'.)

**Early vasospasm** — Early vasospasm (EVSP) is arterial narrowing that is present at the time of or shortly after hospital admission; it is also called ultra early vasospasm, acute cerebral vasoconstriction, and acute arterial spasm [83-85]. Although EVSP is rarely reported, a study that examined data from 3552 patients with aneurysmal SAH enrolled in clinical trials testing the drug tirilazad found that EVSP was present within 48 hours of admission in 339 patients (10 percent) [86]. The following additional observations were made:

- EVSP was significantly more likely in patients with a poor neurologic grade on admission, intracerebral hematoma, larger aneurysm, thick SAH on CT scan, intraventricular hemorrhage, a history of previous SAH, and a history of hypertension.
- EVSP was not associated with delayed cerebral vasospasm, suggesting that the etiology of the two types of vasospasm is different.
- EVSP was associated with cerebral infarction, neurologic worsening, and unfavorable outcome at three months, after adjustment for differences in admission characteristics.

**Cerebral infarction** — Cerebral infarction is a frequent complication of SAH. Hypodense brain lesions on head CT have been noted in 40 to 60 percent of survivors at 3 to 12 months after SAH [4,87,88]. In a case series of 143 patients with acute aneurysmal SAH admitted from 1998 to 2000 at a single center, cerebral infarction defined on CT scan was found in 56 patients (39 percent) [89]. The time from SAH onset to the last CT scan during the acute hospital stay ranged from 5 to 32 days (mean 12 days).

The two most common patterns of infarction in these 56 patients were:
• Single cortical infarcts, typically located near the site of the ruptured aneurysm, in 23 (40 percent)

• Multiple widespread infarcts, often involving bilateral and subcortical regions and frequently located distal to the ruptured aneurysm, in 28 (50 percent)

The most common cause of infarction after SAH is assumed to be vasospasm (see 'Vasospasm' above) [90]. Hypovolemia may add to the risk of cerebral ischemia in the setting of vasospasm [91]. Other mechanisms of ischemia include occlusion (temporary or permanent) of or damage to cerebral arteries during aneurysm surgery, thromboembolism related to turbulent or stagnant aneurysmal blood flow or clip application, and embolism unrelated to SAH.

Hypodense lesions on CT consistent with infarction appear to be more likely with larger volume SAH and poor initial clinical condition [4,87,88,92]. These observations are supported by the results of a study that analyzed CT scans of 156 patients three months after SAH; additional independent risk factors for hypodense lesions included nocturnal occurrence of SAH (between 12:01 and 8:00 AM), fixed symptoms of delayed ischemia, duration of temporary artery occlusion during surgery, and body mass index [93]. The mechanism of increased ischemia risk with nocturnal SAH is unknown.

**Hydrocephalus** — Hydrocephalus (acute and chronic) is a common complication of SAH. In one large series, hydrocephalus was documented by CT scan in 15 percent of patients, 40 percent of whom were symptomatic [94]. Factors associated with an increased risk for hydrocephalus included intraventricular hemorrhage, posterior circulation aneurysms, treatment with antifibrinolytic agents, and a low Glasgow score on presentation. The incidence was also increased in patients with hyponatremia or a history of hypertension. Older age is an additional risk factor.

Hydrocephalus after SAH is thought to be caused by obstruction of cerebrospinal fluid (CSF) flow by blood products or adhesions, or by a reduction of CSF absorption at the arachnoid granulations [95]. The former occurs as an acute complication; the latter tends to occur two weeks or later, and is more likely to be associated with shunt dependence.

Spontaneous improvement occurs in one-half of patients with acute hydrocephalus and impaired consciousness, usually within 24 hours [96]. In the remainder, acute hydrocephalus is associated with increased morbidity and mortality secondary to rebleeding and cerebral infarction [97].

**Increased ICP** — Patients with SAH may develop increased intracranial pressure (ICP) due to a number of factors, including increased cerebrospinal fluid outflow resistance, acute hydrocephalus, hemorrhage volume, reactive hyperemia after hemorrhage, vasoparalysis, and distal cerebral arteriolar vasodilation [98-101]. In a series of 234 patients with SAH who had ICP monitoring, increased ICP occurred during the hospital stay in 54 percent, including 49 percent of those considered to have a good clinical grade (Hunt and Hess grades I to III) [102].

**Seizures** — Seizures at the onset of SAH appear to be an independent risk factor for late seizures and a predictor of poor outcome [103]. One study of 247 patients with SAH found that 7 percent developed new-onset epilepsy (defined as two or more unprovoked seizures after hospital discharge), and these patients had poor functional recovery and quality of life [104]. Associated cerebral infarction and subdural hematoma predicted epilepsy, suggesting that epilepsy in this setting is due to focal rather than diffuse brain injury.
The incidence of late epilepsy (more than two weeks after surgery) after surgical management of SAH is unclear. Multiple studies have cited an incidence of up to 25 percent \[105-107\]. However, the true incidence now may be lower, given advances in surgical management that have occurred since these studies took place. Patients with a poor grade SAH appear to have a higher incidence of late epilepsy \[108\]. (See "Treatment of aneurysmal subarachnoid hemorrhage", section on 'Antiepileptic drug therapy'.)

**Hyponatremia** — Hyponatremia following subarachnoid hemorrhage is relatively common, and is probably mediated by hypothalamic injury. The water retention that leads to hyponatremia is due to increased secretion of antidiuretic hormone, which may result from either the syndrome of inappropriate ADH secretion or, much less often, volume depletion induced by cerebral salt wasting. These issues are discussed separately. (See "Cerebral salt-wasting".)

**Cardiac abnormalities** — Cardiac abnormalities and electrocardiographic (ECG) changes are commonly seen after SAH and appear to be more common and more severe in those with more severe SAH \[109,110\]. The most frequent ECG abnormalities are ST segment depression, QT interval prolongation, deep symmetric T wave inversions, and prominent U waves. Life-threatening rhythm disturbances such as torsades de pointes have also been described, as well as atrial fibrillation and flutter. ST-T wave abnormalities along with bradycardia and relative tachycardia were found in one large series to be independently associated with mortality \[111\]. (See "Cardiac complications of stroke".)

The ECG changes are predominantly reflective of ischemic changes in the subendocardium of the left ventricle. The development of actual myocardial injury (in as many as 20 percent of patients) can be established by elevations of CK-MB or serum troponin I (>0.1 µg/L), which is a specific and more sensitive marker of myocardial necrosis \[110,112\]. Patients with elevated troponin I concentrations are more likely to have ECG abnormalities and clinical evidence of left ventricular dysfunction. Subendocardial ischemia is an independent predictor of poor outcome in patients with SAH and must be managed aggressively (although without the use of aspirin) \[109\]. (See "Troponins and creatine kinase as biomarkers of cardiac injury" and "Overview of the acute management of unstable angina and acute non-ST elevation myocardial infarction".)

A wide spectrum of regional left ventricular wall motion abnormalities, demonstrable by echocardiography, can occur with SAH; these are typically but not always reversible \[110,113,114\]. Some patients develop a pattern of transient apical left ventricular dysfunction that mimics myocardial infarction (but in the absence of significant coronary artery disease), a condition known as takotsubo cardiomyopathy, or transient left ventricular apical ballooning syndrome \[114,115\]. (See "Stress-induced (takotsubo) cardiomyopathy".)

Acute troponin elevation after SAH appears to be associated with increased risk of cardiopulmonary and cerebrovascular complications \[109,116\]. In a series of 253 patients with SAH who had serial troponin measurements for clinical or ECG signs of potential cardiac injury, elevated peak troponin levels were associated with an increased risk of left ventricular dysfunction, pulmonary edema, hypotension requiring pressors, and delayed cerebral ischemia from vasospasm \[116\]. These findings were confirmed in a meta-analysis of 25 studies of SAH including 2960 patients; in this analysis, elevated troponin levels were also associated with increased mortality and worse functional
outcome [109]. (See "Elevated cardiac troponin concentration in the absence of an acute coronary syndrome", section on 'Acute stroke'.)

Elevation of serum brain type natriuretic peptide (BNP) has been noted after SAH [109,117,118], although the source of this elevation is unclear. BNP is present in the brain and in the heart; serum BNP elevation occurs with heart failure. (See "Natriuretic peptide measurement in heart failure and other diseases"). In a prospective cohort of 57 subjects with SAH, elevated BNP levels were associated with the presence of cardiac regional wall motion abnormalities, diastolic dysfunction, pulmonary edema, elevated cardiac troponin I, and left ventricular ejection fraction <50 percent [119]. These findings suggest that BNP is released from patients with cardiac injury after SAH. A meta-analysis that included almost 3000 patients with SAH found that elevated BNP levels were associated with increased mortality [109].

**Mechanisms of myocardial injury** — Myocardial injury is most likely the result of a centrally mediated release of catecholamines within the myocardium due to hypoperfusion of the posterior hypothalamus. In support of this neurocardiogenic hypothesis, a study of 223 patients with SAH found an incremental and independent relationship between the degree of neurologic injury related to SAH and the probability of elevated serum levels of cardiac troponin [120]. In contrast to some previous reports, this study found no association between serum levels of catecholamines and troponin levels.

While the neurocardiogenic hypothesis seems to be the most plausible mechanism, the causes of myocardial damage associated with SAH are likely to be multifactorial and include not only autonomic dysfunction but also factors affecting myocardial oxygen demand, the effect of medications given during treatment, and gender differences [121]. As an example, one small case series found that hypomagnesemia was present in 37 percent of patients with SAH and was related to a prolongation of the PR interval and a shorter QTc interval [122]. (See "Significance of hypomagnesemia in cardiovascular disease").

**DIAGNOSIS** — Sudden "thunderclap" headache, regardless of severity or prior headache history, should raise the clinical suspicion for subarachnoid hemorrhage (SAH) and compel a diagnostic evaluation. Altered consciousness, collapse or vomiting at onset, meningismus, retinal subhyaloid hemorrhages, and a paucity of lateralizing neurologic signs are additional features that are characteristic of SAH. In patients with a suspicious history, the first step is to determine the presence of SAH, followed by an evaluation for the cause of hemorrhage.

The combination of vitreous (preretinal) hemorrhages with SAH is known as Terson's syndrome and implies a poorer prognosis. In a systematic review, patients with Terson's syndrome had higher Hunt and Hess grades (table 3) and significantly higher mortality than those without [123]. The preretinal hemorrhages of Terson's syndrome may indicate a more abrupt increase in intracranial pressure and must be distinguished from the more benign retinal hemorrhages sometimes associated with SAH [124].

Noncontrast head computed tomography (CT), with or without lumbar puncture, is the mainstay of diagnosis of SAH. A negative head CT and lumbar puncture effectively eliminate the diagnosis of SAH as long as both tests are performed within a few days of the event [125]. Nevertheless, cerebral angiography should be considered if diagnostic doubt remains.

**Head CT scan** — The cornerstone of SAH diagnosis is the noncontrast head CT scan [126,127]. Clot is demonstrated in the subarachnoid space in 92 percent of cases if the
scan is performed within 24 hours of the bleed [127,128]. Intracerebral extension is present in 20 to 40 percent of patients and intraventricular and subdural blood may be seen in 15 to 35 and 2 to 5 percent, respectively. The head CT scan should be performed with thin cuts through the base of the brain to increase the sensitivity to small amounts of blood [129].

The distribution of blood on CT (performed within 72 hours after the bleed) is a poor predictor of the site of an aneurysm except in patients with ruptured anterior cerebral artery or anterior communicating artery aneurysms and in patients with a parenchymal hematoma [21].

The sensitivity of head CT for detecting SAH is highest in the first 6 to 12 hours after SAH (nearly 100 percent) and then progressively declines over time to about 58 percent at day five [127,128,130-132]. The sensitivity of head CT is also reduced with more minor bleeds. In one study, for example, a minor SAH was not diagnosed by CT scan in 55 percent of patients; lumbar puncture was positive in all cases [133].

**Lumbar puncture** — Lumbar puncture is mandatory if there is a strong suspicion of SAH despite a normal head CT [126]. The classic findings are an elevated opening pressure and an elevated red blood cell (RBC) count that does not diminish from CSF tube one to tube four. Immediate centrifugation of the CSF can help differentiate bleeding in SAH from that due to a traumatic spinal tap.

**Clearing of blood** — Clearing of blood (a declining RBC count with successive collection tubes) is purported to be a useful way of distinguishing a traumatic LP from SAH. However, this is an unreliable sign of a traumatic tap, since a decrease in the number of RBCs in later tubes can occur in SAH. This method can reliably exclude SAH only if the late or final collection tube is normal. (See "Cerebrospinal fluid: Physiology and utility of an examination in disease states", section on 'Traumatic tap'.)

**Xanthochromia** — Xanthochromia (pink or yellow tint) represents hemoglobin degradation products. An otherwise unexplained xanthochromic supernatant in CSF is highly suggestive of SAH. Xanthochromia may be visually detected by comparing a vial of CSF with a vial of plain water held side by side against a white background in bright light [134].

The utility of xanthochromia and CSF red cell counts is illustrated by a retrospective study of 117 adults with no known history of aneurysm or previous SAH who presented with thunderclap headache in the absence of trauma [135]. All had a negative noncontrast head CT followed by LP. Xanthochromic CSF was found by visual inspection in 18 patients (15 percent). Those patients then had four-vessel catheter angiography, which detected a ruptured cerebral aneurysm in 13 (72 percent). One patient with no xanthochromia had an elevated red blood cell count (≥20,000/microL) in four successive collection tubes and a ruptured aneurysm by angiography. Xanthochromia for the detection of cerebral aneurysms had a sensitivity and specificity of 93 and 95 percent.

The presence of xanthochromia indicates that blood has been in the CSF for at least two hours; lumbar puncture performed before this time may not reveal xanthochromia. Xanthochromia can last for two weeks or more [136,137].

Xanthochromia can also occur with increased CSF concentrations of protein (150 mg/dL), systemic hyperbilirubinemia (serum bilirubin >10 to 15 mg/dL), and traumatic lumbar puncture with more than 100,000 red blood cells/microL.

**Spectrophotometry** — Spectrophotometry detects blood breakdown products as they progress from oxyhemoglobin to methemoglobin and finally to bilirubin.
Bilirubin concentration peaks about 48 hours after SAH onset, and it may last as long as four weeks after major SAH [139].

The sample of CSF to be tested by spectrophotometry should be the one that contains the least amount of blood staining. It should be protected from light and sent immediately to the laboratory for analysis [136,139].

Spectrophotometry for detection of bilirubin is highly sensitive (>95 percent) when LP is done at least 12 hours after SAH [137]. Although xanthochromia is generally confirmed by visual inspection, laboratory confirmation with CSF spectrophotometry is more sensitive and, if available, is recommended by some experts [136,139-142]. This point is illustrated by a study that involved 11 analysts who compared xanthochromic CSF samples using visual and spectrophotometric analysis [141]. The spectrophotometric detection of bilirubin was significantly higher than visual detection in conditions where CSF samples were contaminated by presence of hemolyzed blood, or when CSF samples contained low levels of bilirubin.

Despite a higher sensitivity than visual inspection for the detection of xanthochromia, CSF spectrophotometry has only a low to moderate specificity for the diagnosis of SAH [143].

It should be noted that CSF spectrophotometry is not universally recommended. As a practical matter, spectrophotometry is rarely available in North American hospitals.

**Brain MRI** — Limited data suggest that proton density and FLAIR sequences on brain MRI may be as sensitive as head CT for the acute detection of SAH [144]. In addition, FLAIR and T2* sequences on MRI have a high sensitivity in patients with a subacute presentation of SAH (eg, >4 days from the bleed) [145].

**Misdiagnosis** — Misdiagnosis of SAH is not infrequent, and usually results from three common errors [146]:

- Failure to appreciate the spectrum of clinical presentation associated with SAH (see 'Clinical manifestations' above)
- Failure to obtain a head CT scan or to understand its limitations in diagnosing SAH (see 'Head CT scan' above)
- Failure to perform a lumbar puncture and correctly interpret the results (see 'Lumbar puncture' above)

In a hospital-based series of 482 patients admitted with SAH, initial misdiagnosis occurred in 12 percent [147]. Misdiagnosis was independently associated with small SAH volume, normal mental status at presentation, and right-sided aneurysm location. Failure to obtain a head CT scan at initial contact was the most common error, occurring in 73 percent of misdiagnosed patients. Among SAH patients with normal mental status at first contact (45 percent), the misdiagnosis rate rose to 20 percent and was associated with a nearly four-fold increase in mortality at 12 months as well as increased morbidity among survivors.

Delays in diagnosis of SAH are also common, even in patients with a characteristic history [148], leading to delays in treatment in 25 percent of patients [126] that can worsen outcome.

**IDENTIFYING THE ETIOLOGY** — Once a diagnosis of SAH has been made, the etiology of the hemorrhage must be determined with angiographic studies. Of the available tests, digital subtraction angiography (DSA) is believed to have the highest resolution to detect...
intracranial aneurysms and define their anatomic features and remains the gold standard test for this indication [40].

No angiographic cause of SAH is evident in 14 to 22 percent of cases. It is critical to repeat the angiogram in 4 to 14 days if the initial angiogram is negative, since lesions may be hidden in cisterns packed with fresh hemorrhage. A third angiogram at a period of two to three months is advocated by some, but is probably not necessary. (See "Nonaneurysmal subarachnoid hemorrhage").

**Digital subtraction angiography** — Most responsible lesions can be readily identified using standard cross-sectional imaging techniques coupled with DSA that includes injections of the external carotid circulation and deep cervical branches, which may supply a cryptic dural arteriovenous fistula. Angiographic demonstration of key branch points, including the proximal posterior circulation, is essential to definitively rule out aneurysm.

The morbidity of DSA in patients with SAH is relatively low. In a meta-analysis of three prospective studies, for example, the combined risk of permanent and transient neurologic complications was significantly lower in patients with SAH compared with those with a TIA or stroke (1.8 versus 3.7 percent) [149].

**CT and MR angiography** — CT angiography (CTA) and magnetic resonance angiography (MRA) are noninvasive tests that are useful for screening and presurgical planning. Both CTA and MRA can identify aneurysms 3 to 5 mm or larger with a high degree of sensitivity [150], but they do not achieve the resolution of conventional angiography.

The sensitivity of CTA for the detection of ruptured aneurysms, using conventional angiography or digital subtraction angiography as the gold standard, is 83 to 98 percent [151-156]. Small aneurysms, in particular may not be reliably identified.

As technology improves, the sensitivity and specificity of noninvasive imaging is also likely to improve. [54]. A 2011 meta-analysis of CTA diagnosis of intracranial aneurysms found that, compared with single-detector CTA, use of multidetector CTA was associated with an overall improved sensitivity and specificity for aneurysm detection (both >97 percent) as well as improved detection of smaller aneurysms ≤4 mm in diameter [157]. Another systematic review and meta-analysis restricted to patients with SAH had similar findings [158].

A major advantage of CTA over conventional angiography is the speed and ease by which it can be obtained, often immediately after the diagnosis of SAH is made by head CT when the patient is still in the scanner. CTA is increasingly used as an alternative to angiography in many patients with SAH, thereby avoiding the need for conventional angiography [159,160], and is particularly useful in the acute setting in a rapidly declining patient who needs emergent craniotomy for hematoma evacuation. Furthermore, CTA offers a more practical approach to acute diagnosis than MRA, given the constraints of acute patient management.

**Perimesencephalic hemorrhage** — Some patients with an initially negative angiogram have blood in the cisterns around the midbrain, which reflects a perimesencephalic (nonaneurysmal) pattern of hemorrhage (picture 1) [161-163]. Perimesencephalic hemorrhage accounts for about 10 percent of all cases of SAH.

This pattern is associated with a more favorable prognosis as illustrated in a study of 65 patients with perimesencephalic SAH; no patient rebled, none had delayed cerebral ischemia (compared to 4 of 49 with aneurysmal SAH), and only three (5 percent)
developed clinical signs of acute hydrocephalus [162]. All had a good outcome after three months with none having died or been disabled.

It is believed that this nonaneurysmal pattern of hemorrhage is the result of rupture of a small pial fistula or prepontine vein. In support of a venous origin of bleeding, a study involving 55 patients with perimesencephalic SAH found that these patients were more likely than patients with aneurysmal SAH to have a primitive venous drainage directly into the dural sinuses instead of the vein of Galen [164].

Repeat angiography is probably not necessary in patients with perimesencephalic hemorrhage [163]. One study suggested that angiography may be avoided altogether if CT angiography excludes the presence of a verteobasilar aneurysm in patients with a perimesencephalic pattern of hemorrhage on unenhanced CT [165]. A decision analysis supported omitting invasive angiography in these individuals [166].

Perimesencephalic hemorrhage is discussed in detail separately. (See "Perimesencephalic nonaneurysmal subarachnoid hemorrhage".)

Other tests — A minority of SAH is nonaneurysmal. The causes of these hemorrhages are diverse. This topic is discussed separately. (See "Nonaneurysmal subarachnoid hemorrhage".)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient information: Hemorrhagic stroke (The Basics)"

- Beyond the Basics topics (see "Patient information: Stroke symptoms and diagnosis" and "Patient information: Hemorrhagic stroke treatment")

SUMMARY AND RECOMMENDATIONS

- Most subarachnoid hemorrhages (SAH) are caused by ruptured saccular aneurysms. The causes of nonaneurysmal SAH are diverse. (See "Nonaneurysmal subarachnoid hemorrhage".)

- Aneurysmal SAH occurs at an estimated rate of 3 to 25 per 100,000 population. Most aneurysmal SAH occur between 40 and 60 years of age; however young children and elderly adults can be affected. (See 'Epidemiology' above.)

- Cigarette smoking appears to be the most important preventable risk factor for SAH. Family history, hypertension and moderate to heavy alcohol consumption, and sympathomimetic drug use are other risk factors. Stressful life events have not been convincingly shown to be a risk factor for SAH. (See 'Risk factors' above.)
The overwhelming majority of patients present with a sudden onset severe headache which may be associated with brief loss of consciousness, seizures, nausea or vomiting or meningismus. While not invariable, symptom onset may occur in the setting of physical exertion. (See 'Clinical manifestations' above.)

Sudden onset of headache, regardless of severity or prior headache history, should raise the clinical suspicion for SAH and compel a diagnostic evaluation. (See 'Diagnosis' above.)

Noncontrast head CT reveals the diagnosis in more than 90 percent of cases if performed within 24 hours of bleeding onset. (See 'Head CT scan' above.)

Lumbar puncture is mandatory if there is a strong suspicion of SAH despite a normal head CT. The classic findings are an elevated opening pressure and an elevated red blood cell count that does not diminish from CSF tube one to tube four. Immediate centrifugation of the CSF can help differentiate bleeding in SAH from that due to a traumatic spinal tap. (See 'Lumbar puncture' above.)

Once a diagnosis of SAH has been made, the etiology of the hemorrhage must be determined with vascular imaging. Of the available tests, digital subtraction angiography is believed to have the highest resolution to detect intracranial aneurysms and define their anatomic features and remains the gold standard test for this. (See 'Identifying the etiology' above.)

SAH is associated with a mortality rate as high as 50 percent; many patients die before reaching the hospital. (See 'Complications' above.)

Complications of SAH include rebleeding, vasospasm and delayed cerebral ischemia, hydrocephalus, increased intracranial pressure, seizures, hyponatremia, cardiac abnormalities, and hypothalamic dysfunction and pituitary insufficiency. (See 'Complications' above.)

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130. van der Wee N, Rinkel GJ, Hasan D, van Gijn J. Detection of subarachnoid haemorrhage on early CT: is lumbar puncture still needed after a negative scan? J Neurol Neurosurg Psychiatry 1995; 58:357.


151. Villablanca JP, Hooshi P, Martin N, et al. Three-dimensional helical computerized tomography angioigraphy in the diagnosis, characterization, and management of...


The relationship between stroke of various etiologies and alcohol consumption was evaluated in 26,556 male cigarette smokers; relative risks were adjusted for age, body mass index, serum total cholesterol, number of cigarettes smoked daily, history of diabetes, history of heart disease, education, leisure-time activity, and supplementation with an antioxidant. Systolic blood pressure (SBP) and HDL cholesterol (HDLC) were added separately. Light alcohol intake reduced the risk of a stroke, while moderate and heavy consumption increased the risk. Data from Leppala, JM, Paunio, M, Virtamo, J, et al, Circulation 1999; 100:1209.
Headache and vomiting in stroke subtypes

The frequency of sentinel headache, onset headache, and vomiting in three subtypes of stroke: subarachnoid hemorrhage (SAH), intraparenchymal (intracerebral) hemorrhage (IPH), and ischemic stroke (IS). Onset headache was present in virtually all patients with SAH and about one-half of those with IPH; all of these symptoms were infrequent in patients with IS. Data from: Gorelick PB, Hier DB, Caplan LR, et al, Neurology 1986; 36:1445.
### Fisher grade of cerebral vasospasm risk in subarachnoid hemorrhage

<table>
<thead>
<tr>
<th>Group</th>
<th>Appearance of blood on head CT scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No blood detected</td>
</tr>
<tr>
<td>2</td>
<td>Diffuse deposition or thin layer with all vertical layers (in interhemispheric fissure, insular cistern, ambient cistern) less than 1 mm thick</td>
</tr>
<tr>
<td>3</td>
<td>Localized clot and/or vertical layers 1 mm or more in thickness</td>
</tr>
<tr>
<td>4</td>
<td>Intracerebral or intraventricular clot with diffuse or no subarachnoid blood</td>
</tr>
</tbody>
</table>

### Claassen subarachnoid hemorrhage CT rating scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Head CT criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No SAH or IVH</td>
</tr>
<tr>
<td>2</td>
<td>Minimal SAH and no IVH</td>
</tr>
<tr>
<td>3</td>
<td>Minimal SAH with bilateral IVH</td>
</tr>
<tr>
<td>4</td>
<td>Thick SAH (completely filling one or more cistern or fissure) without bilateral IVH</td>
</tr>
<tr>
<td>5</td>
<td>Thick SAH (completely filling one or more cistern or fissure) with bilateral IVH</td>
</tr>
</tbody>
</table>

Hunt and Hess grading system for patients with subarachnoid hemorrhage

<table>
<thead>
<tr>
<th>Grade</th>
<th>Neurologic status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Asymptomatic or mild headache and slight nuchal rigidity</td>
</tr>
<tr>
<td>2</td>
<td>Severe headache, stiff neck, no neurologic deficit except cranial nerve palsy</td>
</tr>
<tr>
<td>3</td>
<td>Drowsy or confused, mild focal neurologic deficit</td>
</tr>
<tr>
<td>4</td>
<td>Stuporous, moderate or severe hemiparesis</td>
</tr>
<tr>
<td>5</td>
<td>Coma, decerebrate posturing</td>
</tr>
</tbody>
</table>

Perimesencephalic subarachnoid hemorrhage

CT scan demonstrates the typical findings of a nonaneurysmal perimesencephalic subarachnoid hemorrhage. Note the predominance of hemorrhage in the interpeduncular fossa (arrow). Courtesy of Guy Rordorf, MD.