stimulation (widespread cortical destruction), brainstem reflexes are absent (global brainstem damage), and there is complete apnea (destruction of the medulla). Demonstration of apnea requires that the PCO_2 be high enough to stimulate respiration, while PO_2 and bp are maintained. EEG is isoelectric at high gain. The absence of deep tendon reflexes is not required because the spinal cord may remain functional. Special care must be taken to exclude drug toxicity and hypothermia prior to making a diagnosis of brain death. Diagnosis should be made only if the state persists for some agreed-upon period, usually 6–24 h.

For a more detailed discussion, see Josephson SA, Miller BL: Confusion and Delirium, Chap. 34, p. 166, and Ropper AH: Coma, Chap. 328, p. 1771, in HPIM-19.

17 Stroke

Sudden onset of a neurologic deficit from a vascular mechanism: ~85% are ischemic; ~15% are primary hemorrhages (subarachnoid [Chap. 18] and intraparenchymal). An ischemic deficit that resolves rapidly without radiologic evidence of an infarction is termed a *transient ischemic attack* (TIA); 24 h is a commonly used boundary between TIA and stroke, although most TIAs last between 5 and 15 min. Stroke is a leading cause of neurologic disability in adults; 200,000 deaths annually in the United States. Much can be done to limit morbidity and mortality through prevention and acute intervention.

PATHOPHYSIOLOGY

Ischemic stroke can be due to embolic occlusion of large cerebral vessels; source of emboli may be heart, aortic arch, or other arteries such as the internal carotids. Small, deep ischemic lesions are most often related to intrinsic small-vessel disease (lacunar strokes). Low-flow strokes are occasionally seen with severe proximal stenosis and inadequate collaterals challenged by systemic hypotensive episodes. Hemorrhages most frequently result from rupture of aneurysms or small vessels within brain tissue. Variability in stroke recovery is influenced by collateral vessels, blood pressure, and the specific site and mechanism of vessel occlusion; if blood flow is restored prior to significant cell death, the pt may experience only transient symptoms, i.e., a TIA.

CLINICAL FEATURES

Ischemic Stroke

Abrupt and dramatic onset of focal neurologic symptoms is typical. Pts may not seek assistance on their own because they are rarely in pain and may lose appreciation that something is wrong (*anosognosia*). Symptoms reflect the vascular territory involved (Table 17-1). Transient monocular blindness (amaurosis fugax) is a particular form of TIA due to retinal ischemia; pts describe a shade descending over the visual field.

TABLE 17-1 ANATOMIC LOCALIZATION IN STROKE

Signs and Symptoms
Cerebral Hemisphere, Lateral Aspect (Middle Cerebral A.)
Hemiparesis
Hemisensory deficit
Motor aphasia (Broca's)—hesitant speech with word-finding difficulty and preserved comprehension
Sensory aphasia (Wernicke's)—anomia, poor comprehension, jargon speech
Unilateral neglect, apraxias
Homonymous hemianopia or quadrantanopia
Gaze preference with eyes deviated toward side of lesion
Cerebral Hemisphere, Medial Aspect (Anterior Cerebral A.)
Paralysis of foot and leg with or without paresis of arm
Cortical sensory loss over leg
Grasp and sucking reflexes
Urinary incontinence
Gait apraxia
Cerebral Hemisphere, Posterior Aspect (Posterior Cerebral A.)
Homonymous hemianopia
Cortical blindness
Memory deficit
Dense sensory loss, spontaneous pain, dysesthesias, choreoathetosis
Brainstem, Midbrain (Posterior Cerebral A.)
Third nerve palsy and contralateral hemiplegia
Paralysis/paresis of vertical eye movement
Convergence nystagmus, disorientation
Brainstem, Pontomedullary Junction (Basilar A.)
Facial paralysis
Paresis of abduction of eye
Paresis of conjugate gaze
Hemifacial sensory deficit
Horner's syndrome
Diminished pain and thermal sense over half body (with or without face)
Ataxia
Brainstem, Lateral Medulla (Vertebral A.)
Vertigo, nystagmus
Horner's syndrome (miosis, ptosis, decreased sweating)
Ataxia, falling toward side of lesion
Impaired pain and thermal sense over half body with or without face

Lacunar Syndromes (Small-Vessel Strokes)

Most common are:

- Pure motor hemiparesis of face, arm, and leg (internal capsule or pons)
- Pure sensory stroke (ventral thalamus)
- Ataxic hemiparesis (pons or internal capsule)
- Dysarthria—clumsy hand (pons or genu of internal capsule)

Intracranial Hemorrhage

Vomiting and drowsiness occur in some cases with increased intracranial pressure (ICP), and headache is common. Signs and symptoms are often not confined to a

TABLE 17-2 CAUSES OF INTRACRANIAL HEMORRHAGE

Cause	Location	Comments
Head trauma	Intraparenchymal: frontal lobes, anterior temporal lobes; subarachnoid; extra-axial (subdural, epidural)	Coup and contrecoup injury during brain deceleration
Hypertensive hemorrhage	Putamen, globus pallidus, thalamus, cerebellar hemisphere, pons	Chronic hypertension produces hemorrhage from small (~30–100 μm) vessels in these regions
Transformation of prior ischemic infarction	Basal ganglion, subcortical regions, lobar	Occurs in 1–6% of ischemic strokes with predilection for large hemispheric infarctions
Metastatic brain tumor	Lobar	Lung, choriocarcinoma, melanoma, renal cell carcinoma, thyroid, atrial myxoma
Coagulopathy	Any	Risk for ongoing hematoma expansion
Drug	Any, lobar, subarachnoid	Cocaine, amphetamine
Arteriovenous malformation	Lobar, intraventricular, subarachnoid	Risk is ~2–3% per year for bleeding if previously unruptured
Aneurysm	Subarachnoid, intraparenchymal, rarely subdural	Mycotic and nonmycotic forms of aneurysms
Amyloid angiopathy	Lobar	Degenerative disease of intracranial vessels; associated with dementia, rare in patients <60 years
Cavernous angioma	Intraparenchymal	Multiple cavernous angiomas linked to mutations in *KRIT1*, *CCM2*, and *PDCD10* genes
Dural arteriovenous fistula	Lobar, subarachnoid	Produces bleeding by venous hypertension
Capillary telangiectasias	Usually brainstem	Rare cause of hemorrhage

single vascular territory. Etiologies are diverse but hypertension related is the most common (Table 17-2). Hypertensive hemorrhages typically occur in the following locations:

- Putamen: contralateral hemiparesis often with homonymous hemianopia
- Thalamus: hemiparesis with prominent sensory deficit
- Pons: quadriplegia, "pinpoint" pupils, impaired horizontal eye movements
- Cerebellum: headache, vomiting, gait ataxia

A neurologic deficit that evolves gradually over 30–90 min strongly suggests intracerebral bleeding.

TREATMENT STROKE

Principles of management are outlined in Fig. 17-1. Stroke needs to be distinguished from potential mimics, including seizure, migraine, tumor, and metabolic derangements.

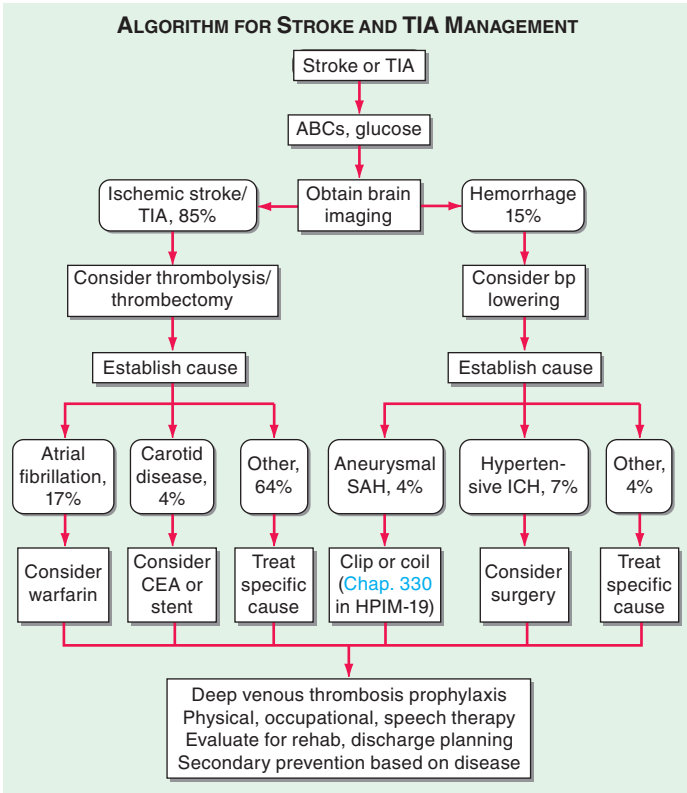

FIGURE 17-1 Medical management of stroke and TIA. *Rounded boxes* are diagnoses; *rectangles* are interventions. Numbers are percentages of stroke overall. ABCs, airway, breathing, circulation; bp, blood pressure; CEA, carotid endarterectomy; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; TIA, transient ischemic attack.

- Imaging. After initial stabilization, an emergency noncontrast head CT scan is necessary to differentiate ischemic from hemorrhagic stroke. With large ischemic strokes, CT abnormalities are usually evident within the first few hours, but small infarcts can be difficult to visualize by CT. CT or MR angiography (CTA/MRA) may help reveal vascular occlusions. Diffusion-weighted MRI has a high sensitivity for identifying ischemic stroke even minutes after onset.

ACUTE ISCHEMIC STROKE Treatments designed to reverse or lessen tissue infarction include: (1) medical support, (2) intravenous thrombolysis, (3) endovascular revascularization, (4) antiplatelet agents, (5) anticoagulation, and (6) neuroprotection.

MEDICAL SUPPORT Optimize perfusion in ischemic penumbra surrounding the infarct.

- Blood pressure should never be lowered precipitously (exacerbates the underlying ischemia), and only in the most extreme situations should gradual lowering

be undertaken (e.g., malignant hypertension with bp > 220/120 mmHg or, if thrombolysis planned, bp > 185/110 mmHg).

- Intravascular volume should be maintained with isotonic fluids because volume restriction is rarely helpful. Osmotic therapy with mannitol may be necessary to control edema in large infarcts, but isotonic volume must be replaced to avoid hypovolemia.
- In cerebellar infarction (or hemorrhage), rapid deterioration can occur from brainstem compression and hydrocephalus, requiring neurosurgical intervention.

INTRAVENOUS THROMBOLYSIS

- Ischemic deficits of <3 h duration, with no hemorrhage by CT criteria, may benefit from thrombolytic therapy with IV recombinant tissue plasminogen activator (Table 17-3).
- Based on trial data, IV rtPA is used in many centers for deficits of 3–4.5 h duration, but is not yet approved for this window in the United States.

TABLE 17-3 ADMINISTRATION OF INTRAVENOUS RTPA FOR AIS[a]

Indication	Contraindication
Clinical diagnosis of stroke	Sustained bp >185/110 mmHg despite treatment
Onset of symptoms to time of drug administration ≤4.5 h[b]	Platelets <100,000; Hct <25%; glucose <50 or >400 mg/dL
CT scan showing no hemorrhage or edema of >1/3 of the MCA territory	Use of heparin within 48 h and prolonged PTT, or elevated INR
Age 18 ≥ years	Rapidly improving symptoms
Consent by patient or surrogate	Prior stroke or head injury within 3 months; prior intracranial hemorrhage
	Major surgery in preceding 14 days
	Minor stroke symptoms
	Gastrointestinal bleeding in preceding 21 days
	Recent myocardial infarction
	Coma or stupor
Administration of rtPA	
IV access with two peripheral IV lines (avoid arterial or central line placement).	
Review eligibility for rtPA.	
Administer 0.9 mg/kg IV (maximum 90 mg) IV as 10% of total dose by bolus, followed by remainder of total dose over 1 h.	
Frequent cuff blood pressure monitoring.	
No other antithrombotic treatment for 24 h.	
For decline in neurologic status or uncontrolled blood pressure, stop infusion, give cryoprecipitate, and reimage brain emergently.	
Avoid urethral catheterization for ≥2 h.	

[a]See Activase (tissue plasminogen activator) package insert for complete list of contraindications and dosing.

[b]Depending on the country, IV rtPA may be approved for up to 4.5 h with additional restrictions.

Abbreviations: AIS, acute ischemic stroke; INR, international normalized ratio; MCA, middle cerebral artery; rtPA, recombinant tissue plasminogen activator; PTT, partial thromboplastin time.

ENDOVASCULAR REVASCULARIZATION

- Ischemic stroke from large-vessel intracranial occlusion results in high rates of morbidity and mortality; pts with such occlusions likely benefit from embolectomy (<6 h duration) administered at the time of an urgent cerebral angiogram at specialized centers. CT angiography is becoming more commonly used as part of initial imaging protocols to identify these patients rapidly.

ANTIPLATELET AGENTS

- Aspirin (up to 325 mg/d) is safe and has a small but definite benefit in acute ischemic stroke.

ANTICOAGULATION

- Trials do not support the use of heparin or other anticoagulants acutely for pts with acute stroke.

NEUROPROTECTION

- Hypothermia is effective in coma following cardiac arrest but has not been shown to benefit stroke patients. Other neuroprotective agents have shown no efficacy in human trials despite promising animal data.

STROKE CENTERS AND REHABILITATION

- Pt care in comprehensive stroke units followed by rehabilitation services improves neurologic outcomes and reduces mortality.

ACUTE INTRACEREBRAL HEMORRHAGE

- Noncontrast head CT will confirm diagnosis.
- Rapidly identify and correct any coagulopathy.
- 35–45% of pts die in the first month; prognosis is determined by volume and location of hematoma.
- Stuporous or comatose pts generally are treated presumptively for elevated ICP. Treatment for edema and mass effect with osmotic agents may be necessary; glucocorticoids not helpful.
- Neurosurgical consultation should be sought for possible urgent evacuation of cerebellar hematoma; in other locations, data do not support surgical intervention.

EVALUATION: DETERMINING THE CAUSE OF STROKE

Although initial management of acute ischemic stroke or TIA does not depend on the etiology, establishing a cause is essential to reduce risk of recurrence (Table 17-4); particular attention should be on atrial fibrillation and carotid atherosclerosis because these etiologies have proven secondary prevention strategies. Nearly 30% of strokes remain unexplained despite extensive evaluation.

Clinical examination should be focused on the peripheral and cervical vascular system. Routine studies include CXR and ECG, urinalysis, CBC/platelets, electrolytes, glucose, ESR, lipid profile, PT, and PTT. If a hypercoagulable state is suspected, further studies of coagulation are indicated.

Imaging evaluation may include brain MRI (compared with CT, increased sensitivity for small infarcts of cortex and brainstem); MR or CT angiography (evaluate patency of intracranial vessels and extracranial carotid and vertebral vessels); noninvasive carotid ultrasound; or cerebral angiography ("gold standard" for evaluation of intracranial and extracranial vascular disease). For suspected cardiogenic source, cardiac echocardiogram with attention to right-to-left shunts, and inpatient cardiac telemetry and long-term cardiac event monitoring indicated.

TABLE 17-4 CAUSES OF ISCHEMIC STROKE

Common Causes	Uncommon Causes
Thrombosis	Hypercoagulable disorders
Lacunar stroke (small vessel)	Protein C deficiency[a]
Large-vessel thrombosis	Protein S deficiency[a]
Dehydration	Antithrombin III deficiency[a]
Embolic occlusion	Antiphospholipid syndrome
Artery-to-artery	Factor V Leiden mutation[a]
Carotid bifurcation	Prothrombin G20210 mutation[a]
Aortic arch	Systemic malignancy
Arterial dissection	Sickle cell anemia
Cardioembolic	β Thalassemia
Atrial fibrillation	Polycythemia vera
Mural thrombus	Systemic lupus erythematosus
Myocardial infarction	Homocysteinemia
Dilated cardiomyopathy	Thrombotic thrombocytopenic purpura
Valvular lesions	Disseminated intravascular coagulation
Mitral stenosis	Dysproteinemias[a]
Mechanical valve	Nephrotic syndrome[a]
Bacterial endocarditis	Inflammatory bowel disease[a]
Paradoxical embolus	Oral contraceptives
Atrial septal defect	Venous sinus thrombosis[b]
Patent foramen ovale	Fibromuscular dysplasia
Atrial septal aneurysm	Vasculitis
Spontaneous echo contrast	Systemic vasculitis (PAN, granulomatosis with polyangiitis [Wegener's], Takayasu's, giant cell arteritis)
Stimulant drugs: cocaine, amphetamine	Primary CNS vasculitis
	Meningitis (syphilis, tuberculosis, fungal, bacterial, zoster)
	Noninflammatory vasculopathy
	Reversible vasoconstriction syndrome
	Fabry's disease
	Angiocentric lymphoma
	Cardiogenic
	Mitral valve calcification
	Atrial myxoma
	Intracardiac tumor
	Marantic endocarditis
	Libman-Sacks endocarditis
	Subarachnoid hemorrhage vasospasm
	Moyamoya disease
	Eclampsia

[a]Chiefly cause venous sinus thrombosis.
[b]May be associated with any hypercoagulable disorder.
Abbreviations: PAN, polyarteritis nodosa.

PRIMARY AND SECONDARY PREVENTION OF STROKE

Risk Factors

Atherosclerosis is a systemic disease affecting arteries throughout the body. Multiple factors including hypertension, diabetes, hyperlipidemia, and family history influence stroke and TIA risk (Table 17-5). Cardioembolic risk factors include atrial fibrillation/flutter, MI, valvular heart disease, and cardiomyopathy. Hypertension and diabetes are also specific risk factors for lacunar stroke and intraparenchymal hemorrhage. Smoking is a potent risk factor for all vascular mechanisms of stroke. *Identification of modifiable risk factors and prophylactic interventions to lower risk is probably the best approach to stroke overall.*

Antiplatelet Agents

Platelet antiaggregation agents can prevent atherothrombotic events, including TIA and stroke, by inhibiting formation of intraarterial platelet aggregates. Aspirin (50–325 mg/d) inhibits thromboxane A_2, a platelet aggregating and vasoconstricting prostaglandin. Aspirin, clopidogrel (blocks the platelet adenosine diphosphate [ADP] receptor), and the combination of aspirin plus extended-release dipyridamole (inhibits platelet uptake of adenosine) are the antiplatelet agents most commonly used. In general, antiplatelet agents reduce new stroke events by 25–30%. Every pt who has experienced an atherothrombotic stroke or TIA and has no contraindication

TABLE 17-5 RECOMMENDATIONS ON CHRONIC USE OF ANTITHROMBOTICS FOR VARIOUS CARDIAC CONDITIONS

Condition	Recommendation
Nonvalvular atrial fibrillation	Calculate CHADS2[a] score
• CHADS2 score 0	Aspirin or no antithrombotic
• CHADS2 score 1	Aspirin or OAC
• CHADS2 score >1	OAC
Rheumatic mitral valve disease	
• With atrial fibrillation, previous embolization, or atrial appendage thrombus, or left atrial diameter >55 mm	OAC
• Embolization or appendage clot despite OAC	OAC plus aspirin
Mitral valve prolapse	
• Asymptomatic	No therapy
• With otherwise cryptogenic stroke or TIA	Aspirin
• Atrial fibrillation	OAC
Mitral annular calcification	
• Without atrial fibrillation but systemic embolization, or otherwise cryptogenic stroke or TIA	Aspirin
• Recurrent embolization despite aspirin	OAC
• With atrial fibrillation	OAC
Aortic valve calcification	
• Asymptomatic	No therapy
• Otherwise cryptogenic stroke or TIA	Aspirin
Aortic arch mobile atheroma	
• Otherwise cryptogenic stroke or TIA	Aspirin or OAC
Patent foramen ovale	
• Otherwise cryptogenic ischemic stroke or TIA	Aspirin
• Indication for OAC (deep venous thrombosis or hypercoagulable state)	OAC

(*Continued*)

TABLE 17-5 RECOMMENDATIONS ON CHRONIC USE OF ANTITHROMBOTICS FOR VARIOUS CARDIAC CONDITIONS (*CONTINUED*)

Condition	Recommendation
Mechanical heart value	
• Aortic position, bileaflet or Medtronic Hall tilting disk with normal left atrial size and sinus rhythm	VKA INR 2.5, range 2–3
• Mitral position tilting disk or bileaflet valve	VKA INR 3.0, range 2.5–3.5
• Mitral or aortic position, anterior-apical myocardial infarct, or left atrial enlargement	VKA INR 3.0, range 2.5–3.5
• Mitral or aortic position, with atrial fibrillation, or hypercoagulable state, or low ejection fraction, or atherosclerotic vascular disease	Aspirin plus VKA INR 3.0, range 2.5–3.5
• Systemic embolization despite target INR	Add aspirin and/or increase INR: prior target was 2.5 increase to 3.0, range 2.5–3.5; prior target was 3.0 increase to 3.5, range 3–4
Bioprosthetic valve	
• No other indication for VKA therapy	Aspirin
Infective endocarditis	Avoid antithrombotic agents
Nonbacterial thrombotic endocarditis	
• With systemic embolization	Full-dose unfractionated heparin or SC LMWH

[a]CHADS2 score calculated as follows: 1 point for age >75 years, 1 point for hypertension, 1 point for congestive heart failure, 1 point for diabetes, and 2 points for stroke or TIA; sum of points is the total CHADS2 score.
Note: Dose of aspirin is 50–325 mg/d; target INR for OAC is between 2 and 3 unless otherwise specified.
Abbreviations: INR, international normalized ratio; LMWH, low-molecular-weight heparin; OAC, oral anticoagulant (VKA, thrombin inhibitor, oral factor Xa inhibitors); TIA, transient ischemic attack; VKA, vitamin K antagonist.
Sources: Modified from DE Singer et al: *Chest* 133:546S, 2008; DN Salem et al: *Chest* 133:593S, 2008.

should take an antiplatelet agent regularly because the average annual risk of another stroke is 8–10%. The choice of aspirin, clopidogrel, or dipyridamole plus aspirin must balance the fact that the latter are marginally more effective than aspirin but the cost is higher.

Embolic Stroke

In pts with atrial fibrillation and stroke, anticoagulants are generally the treatment of choice.

Anticoagulation Therapy for Noncardiogenic Stroke

Data do not support the use of long-term warfarin for preventing atherothrombotic stroke for either intracranial or extracranial cerebrovascular disease.

Carotid Revascularization

Carotid endarterectomy benefits many pts with *symptomatic* severe (>70%) *carotid stenosis*; the relative risk reduction is ~65%. However, if the perioperative stroke

rate is >6% for any surgeon, the benefit is questionable. Endovascular stenting is an emerging option; there remains controversy as to who should receive a stent or undergo endarterectomy. Surgical results in pts with *asymptomatic carotid stenosis* are less robust, and medical therapy for reduction of atherosclerosis risk factors plus antiplatelet medications is generally recommended in this group.

For a more detailed discussion, see Smith WS, Johnston SC, Hemphill JC III: Cerebrovascular Diseases, Chap. 446, p. 2559, in HPIM-19.

18 Subarachnoid Hemorrhage

Excluding head trauma, the most common cause of subarachnoid hemorrhage (SAH) is rupture of an intracranial (saccular) aneurysm; other etiologies include bleeding from a vascular malformation (arteriovenous malformation or dural arteriovenous fistula) and extension into the subarachnoid space from a primary intracerebral hemorrhage. Approximately 2% of the population harbor aneurysms, and 25,000–30,000 cases of aneurysmal rupture producing SAH occur each year in the United States; rupture risk for aneurysms <10 mm in size is 0.1% per year; for unruptured aneurysms, the surgical morbidity rate far exceeds the percentage.

CLINICAL PRESENTATION

Sudden, severe headache, often with transient loss of consciousness at onset; vomiting is common. Bleeding may injure adjacent brain tissue and produce focal neurologic deficits. A progressive third nerve palsy, usually involving the pupil, along with headache, suggests posterior communicating artery aneurysm. In addition to dramatic presentations, aneurysms can undergo small ruptures with leaks of blood into the subarachnoid space (sentinel bleeds). The initial clinical manifestations of SAH can be graded using established scales (Table 18-1); prognosis for good outcome falls as the grade increases.

INITIAL EVALUATION

- Noncontrast CT is initial study of choice and usually demonstrates hemorrhage if obtained within 72 h. LP is required for diagnosis of suspected SAH if CT is nondiagnostic; xanthochromia of the spinal fluid is seen within 6–12 h after rupture and lasts for 1–4 weeks.
- Cerebral angiography is necessary to localize and define the anatomic details of the aneurysm and to determine if other unruptured aneurysms exist; angiography should be performed as soon as possible after diagnosis of SAH.
- ECG may reveal ST-segment and T-wave changes similar to cardiac ischemia; caused by circulating catecholamines and excessive discharge of sympathetic neurons. A reversible cardiomyopathy producing shock or congestive heart failure may result.
- Studies of coagulation and platelet count should be obtained, with rapid correction indicated if SAH is documented.