Chapter 13: Stroke

INTRODUCTION

- *Stroke* involves the abrupt onset of focal neurologic dysfunction that lasts at least 24 hours and is caused by cerebral, spinal, or retinal infarction. Stroke can be either ischemic or hemorrhagic. Transient ischemic attacks (TIAs) are focal ischemic neurologic deficits lasting <24 hours and usually <30 minutes.

PATHOPHYSIOLOGY

Ischemic Stroke

- Ischemic stroke (87% of all strokes) results from occlusion of a cerebral artery that reduces cerebral blood flow. Ischemic strokes are due either to local thrombus formation or emboli from a distant site. Atherosclerosis of large intracranial or extracranial arteries or small artery disease can result in ischemic stroke. Emboli can arise from the heart in patients with atrial fibrillation, valvular heart disease, or other prothrombotic heart problems and cause about 25% of ischemic strokes. The stroke cause is undetermined in some cases.
- Decreased cerebral blood flow can lead to infarction of cerebral tissue with a surrounding area that is ischemic but may maintain membrane integrity (the ischemic penumbra). This penumbra is an area of brain tissue that is potentially salvageable with urgent pharmacologic and endovascular treatment interventions.
- Insufficient oxygen supply in ischemic tissue leads to adenosine triphosphate (ATP) depletion with lactate buildup due to anaerobic metabolism and accumulation of intracellular sodium and water, leading to cytotoxic edema and eventual cell lysis. An influx of calcium intracellularly activates lipases and proteases, resulting in protein degradation and free fatty acid release from cellular membranes. Release of excitatory amino acids (eg, glutamate, aspartate) in ischemic tissue perpetuates neuronal damage and produces damaging prostaglandins, leukotrienes, and reactive oxygen species. These processes occur within 2–3 hours of the onset of ischemia and ultimately lead to cellular apoptosis and necrosis.
- The most common modifiable risk factors for ischemic stroke include hypertension, cigarette smoking, diabetes, atrial fibrillation, and dyslipidemia.

Hemorrhagic Stroke

- Hemorrhagic strokes (13% of strokes) include subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH). SAH may result from trauma or rupture of an intracranial aneurysm or arteriovenous malformation (AVM). ICH occurs when bleeding in the brain parenchyma results in hematoma formation.
- Intracranial hematoma causes mechanical compression of brain parenchyma. Early hematoma expansion often occurs within 3 hours of hemorrhage onset, contributing to worsened functional outcome and increased mortality.
- Secondary mechanisms of injury are mediated by the subsequent inflammatory response, cerebral edema, and damage from blood product degradation.

CLINICAL PRESENTATION

- Patients may be unable to provide a reliable history because of cognitive or language deficits. Family members or other witnesses may need to provide this information.

- Symptoms include unilateral weakness, inability to speak, loss of vision, vertigo, or falling. Ischemic stroke is not usually painful, but some patients complain of headache. Pain and headache are more common and severe in hemorrhagic stroke.
- Neurologic deficits on physical examination depend on the brain area involved. Hemi- or monoparesis and hemisensory deficits are common. Patients with posterior circulation involvement may have vertigo and diplopia. Anterior circulation strokes commonly result in aphasia. Patients may experience dysarthria, visual field defects, and altered levels of consciousness.

DIAGNOSIS

- Blood glucose, platelet count, and coagulation parameters (eg, prothrombin time, aPTT) are used in stroke assessment to determine treatment eligibility.
- Tests for hypercoagulable states (protein C and S deficiency, antiphospholipid antibody) should be done only when the etiology cannot be determined based on presence of well-known risk factors.
- Computed tomography (CT) and magnetic resonance imaging (MRI) head scans can reveal areas of hemorrhage and infarction.
- Vascular imaging with computed tomography angiography (CTA) is recommended in patients with endovascular treatment indications.
- Carotid Doppler (CD), electrocardiogram (ECG), transthoracic echocardiogram (TTE), and transcranial Doppler (TCD) studies can each provide valuable diagnostic information.

TREATMENT

- Goals of Treatment: The goals are to: (1) reduce ongoing neurologic injury acutely to reduce mortality and long-term disability; (2) prevent complications secondary to immobility and neurologic dysfunction; and (3) prevent stroke recurrence.

General Approach

- Ensure adequate respiratory and cardiac support and determine quickly from CT scan whether the lesion is ischemic or hemorrhagic.
- Evaluate ischemic stroke patients presenting within hours of symptom onset for pharmacologic and mechanical reperfusion therapy.
- Patients with TIA require urgent assessment and intervention to reduce the risk of stroke, which is highest in the first few days after TIA.
- Assess patients with hemorrhagic stroke to determine whether they are candidates for surgical intervention.
- After the acute phase, focus on preventing progressive deficits, minimizing complications, and instituting secondary prevention strategies.

Nonpharmacologic Therapy

Ischemic Stroke

- Endovascular intervention and thrombectomy with retrievable stents to reperfuse ischemic brain tissue is recommended by the American Heart Association (AHA) and American Stroke Association (ASA). Thrombectomy is strongly recommended for patients with anterior circulation occlusion in the internal carotid artery (ICA) or the M1 segment of the middle cerebral artery (MCA) who are within 6 hours of symptom onset and may be considered in select patients within 6–24 hours of symptom onset. The benefit of mechanical thrombectomy is less clear in posterior circulation occlusions and should be considered on a case-by-case basis.
- Decompressive hemicraniectomy is a surgical procedure to reduce intracranial pressure (typically due to cerebral edema) and can reduce mortality and improve functional outcome in select patients.
- For all ischemic stroke patients, coordinated care with a multidisciplinary approach to assessment and early rehabilitation reduces overall disability due to stroke.

- In secondary prevention, carotid endarterectomy of an ulcerated or stenotic carotid artery is effective in reducing stroke incidence and recurrence in appropriate patients and in centers where operative morbidity and mortality are low. In patients younger than age 70, carotid stenting is a less invasive alternative and can reduce recurrent stroke risk when combined with aspirin and clopidogrel therapy.

Hemorrhagic Stroke

- In SAH from ruptured intracranial aneurysm or AVM, early intervention with either surgical clipping or endovascular coiling of the vascular abnormality reduces mortality from rebleeding.
- Early surgical intervention and hematoma removal is recommended for patients with cerebellar hemorrhage and neurologic deterioration, brainstem compression, or hydrocephalus from ventricular obstruction. The usefulness of surgical hematoma evacuation is not well established for patients with cerebral hemorrhage.
- Ventricular drainage with an extraventricular drain (EVD) is reasonable in patients with hydrocephalus causing decreased consciousness.

Temperature Management

- Fever worsens outcomes in patients with both hemorrhagic and ischemic stroke. Identification of the source and pharmacologic and/or nonpharmacologic management is recommended to maintain normothermia range. Because of limited supporting data, induced hypothermia should be done only in the setting of controlled, clinical trials.

Pharmacologic Therapy of Ischemic Stroke

- **Table 13-1** provides evidence-based recommendations for pharmacotherapy of ischemic stroke.
- **Alteplase** initiated within 4.5 hours of symptom onset improves functional ability after ischemic stroke. Adherence to a guideline-recommended protocol is essential to achieving positive outcomes: (1) activate the stroke team; (2) obtain CT scan to rule out hemorrhage; (3) treat as early as possible within 4.5 hours of symptom onset; (4) meet all inclusion criteria with no contraindications (**Table 13-2**); (5) administer alteplase 0.9 mg/kg IV total dose (maximum 90 mg), with 10% infused as an initial bolus over 1 minute and the remainder given over 1 hour; (6) avoid anticoagulant and antiplatelet therapy for 24 hours after alteplase; and (7) monitor the patient closely for elevated blood pressure (BP), neurologic status, and hemorrhage.
- **Aspirin** 160–325 mg/day started within 24–48 hours of symptom onset (and 24 hours after alteplase completion) reduces long-term death and disability. An alternate antiplatelet agent may be considered for patients with aspirin allergy or other severe contraindications.
- For patients with elevated BP who are eligible for alteplase, treatment to a goal BP <185/110 mm Hg is recommended before thrombolytic administration. While data are limited, it is also reasonable to maintain BP <185/110 mm Hg for patients undergoing mechanical thrombectomy. For patients not requiring IV thrombolysis or endovascular intervention, BP is often allowed to rise as high as 220/120 mm Hg for the first 48–72 hours because early BP reduction does not prevent death or improve the level of dependency. For patients with comorbid conditions requiring BP management, a reduction of 15% is probably safe. If BP is treated, short-acting and easily titrated IV agents are preferred:
    - ✔ **Labetalol:** 10–20 mg IV over 1–2 minutes; may repeat
    - ✔ **Nicardipine:** 5 mg/hr IV; titrate up by 2.5 mg/hr every 5–15 minutes; maximum 15 mg/hr
    - ✔ **Clevidipine:** 1–2 mg/hr IV; titrate by doubling the dose every 2–5 minutes; maximum 21 mg/hr
    - ✔ Other potential agents: **hydralazine, enalaprilat, nitroprusside** IV infusion, labetalol IV infusion
- Use of urgent anticoagulation (eg, unfractionated heparin or low-molecular-weight heparin) is not routinely recommended in the early phase of acute ischemic stroke treatment. Use of immediate anticoagulation for nonstroke indications (eg, prophylaxis of venous thromboembolism) should be weighed against the risk of intracranial hemorrhagic conversion.

- Secondary prevention of ischemic stroke:

  ✔ All patients who have had an acute ischemic stroke or TIA should receive long-term antithrombotic therapy for secondary prevention. Antiplatelet therapy should be used in noncardioembolic stroke; **aspirin**, **extended-release dipyridamole plus aspirin**, and **clopidogrel** are all first-line agents (**Table 13-1**). Studies of the combination of clopidogrel plus ASA have shown conflicting results on reduction of recurrent stroke, and some found an increase in hemorrhagic events.

  ✔ For patients with atrial fibrillation and a presumed cardiac source of embolism for stroke or TIA, oral anticoagulation with a vitamin K antagonist (**warfarin**), **apixaban**, **dabigatran**, **edoxaban**, or **rivaroxaban** is recommended.

  ✔ Adults with previously treated hypertension who experience a stroke or TIA should be restarted on antihypertensive treatment after the first few days of the index event to reduce the risk of recurrent stroke and other vascular events. Useful options include a **thiazide diuretic**, **angiotensin-converting enzyme (ACE) inhibitor**, **angiotensin receptor blocker**, or combination treatment with a thiazide plus ACE inhibitor. Selection of specific drugs should be individualized based on patient comorbidities. Adults not previously treated for hypertension who experience a stroke or TIA and have a BP ≥140/90 mm Hg should be prescribed antihypertensive treatment several days after the index event. A reasonable goal BP for patients who experienced a stroke or TIA is <130/80 mm Hg.

  ✔ **Statin** therapy is recommended to prevent stroke recurrence in all ischemic stroke patients regardless of baseline lipid levels. Patients ≤75 years of age experiencing ischemic stroke of presumed atherosclerotic origin should be treated with high-intensity statin therapy with a target of achieving ≥50% reduction in low-density lipoprotein (LDL) cholesterol. For patients older than age 75, moderate- or high-intensity statin therapy can be initiated as tolerated. **Ezetimibe** may be added for patients taking maximally tolerated statin therapy but with LDL cholesterol ≥70 mg/dL (1.81 mmol/L). A **proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor** may be considered in very high-risk patients who are taking maximally tolerated statins and ezetimibe with LDL cholesterol ≥70 mg/dL (1.81 mmol/L).

TABLE 13-1

Recommendations for Pharmacotherapy of Ischemic Stroke

	Recommendation	Evidence[a]
Acute treatment	Alteplase 0.9 mg/kg IV (maximum 90 mg), 10% as a bolus with remainder given over 1 hour in select patients within 3 hours of onset	IA
	Alteplase 0.9 mg/kg IV (maximum 90 mg), 10% as a bolus with remainder given over 1 hour in select patients between 3 and 4.5 hours of onset	IB
	Aspirin 160–325 mg daily started within 48 hours of onset	IA
Secondary prevention		
Noncardioembolic	Antiplatelet therapy	
	Aspirin 50–325 mg daily	IA
	Aspirin 25 mg + extended-release dipyridamole 200 mg twice daily	IB
	Clopidogrel 75 mg daily	IIaB
Cardioembolic (especially atrial fibrillation)	Anticoagulant therapy	
	Vitamin K antagonist (warfarin; target INR = 2.5)	IA
	Apixaban 5 mg twice daily	IA
	Dabigatran 150 mg twice daily	IB
	Edoxaban 60 mg daily	—[b]
	Rivaroxaban 20 mg daily	IIaB
Age ≤75 years	High-intensity statin therapy	IB
Age >75 years	Moderate- or high-intensity statin therapy	IIaB-R
BP >140/90 mm Hg	BP reduction	IB-R

[a]Classes: I, evidence or general agreement about usefulness and effectiveness; II, conflicting evidence about usefulness; IIa, weight of evidence in favor of the treatment; IIb, usefulness less well established; III, not useful and maybe harmful. Levels of evidence: A, multiple randomized clinical trials; B, a single randomized trial or nonrandomized studies; C, expert opinion or case studies; B-R, moderate-quality evidence from one or more randomized controlled trials or meta-analyses of moderate-quality randomized controlled trials.

[b]Not graded in current guidelines.

INR, international normalized ratio; IV, intravenous.

TABLE 13-2

Inclusion Criteria and Contraindications to Alteplase Use in Acute Ischemic Stroke

Inclusion criteria • Age 18 years or older • Clinical diagnosis of ischemic stroke with neurologic deficit • Time of symptom onset well established to be <4.5 hours before treatment would begin
Contraindications • Symptoms/imaging consistent with SAH or acute intracerebral hemorrhage • Current use of direct thrombin inhibitors or direct factor Xa inhibitors in prior 48 hours • Use of treatment-dose low-molecular-weight heparin in prior 24 hours • Infective endocarditis • Intra-axial, intracranial neoplasm • Aortic arch dissection • Active internal bleeding or coagulopathy (platelets <100,000/mm^3 [100 × 10^9/L], INR>1.7, aPTT >40 sec, PT >15 sec) • Severe head trauma in prior 3 months • Gastrointestinal malignancy or bleeding within prior 21 days
Warnings/Use Clinical Judgment • History of intracranial hemorrhage • History of ischemic stroke within prior 3 months • Unruptured/unsecured AVM or aneurysm >10 mm • Major surgery or nonhead trauma • History of bleeding diathesis • Extensive regions of clear hypoattenuation on initial CT scan

aPTT, activated partial thromboplastin time; AVM, arteriovenous malformation; CT, computed tomography; INR, international normalized ratio; PT, prothrombin time; SAH, subarachnoid hemorrhage; TT, thrombin time.

Pharmacologic Therapy of Hemorrhagic Stroke

- The usefulness of pharmacotherapy is limited in spontaneous ICH.
- Because hypertension in hemorrhagic stroke increases the risk of hematoma expansion, it is reasonable for patients with a systolic BP >220 mm Hg to receive aggressive BP lowering with continuous IV infusion medications. Acute lowering of systolic BP to a goal of 140 mm Hg is safe and may improve functional outcome. For patients with SAH due to aneurysm rupture, BP control to at least a systolic BP <160 mm Hg is reasonable in the period from symptom onset to aneurysm obliteration.
- When intracranial hemorrhage occurs in a patient on anticoagulants, use of reversal agents to correct the medication-induced coagulopathy should be considered (**Table 13-3**).

TABLE 13-3

Select Anticoagulant Reversal

Drug	First-Line Reversal Recommendation	Alternate Treatment
Warfarin	Vitamin K 10 mg IV × 1 -and- 4PCC INR 2 to <4: 25 units/kg, max 2500 units INR 4–6: 35 units/kg, max 3500 units INR >6: 50 units/kg, max 5000 units	Vitamin K 10 mg IV × 1 -and- FFP 10–15 mL/kg
Dabigatran	Idarucizumab 5 g IV × 1	Hemodialysis 4PCC 50 units/kg
Rivaroxaban ≤10 mg	Andexanet alfa 400 mg IV bolus at rate of 30 mg/min, followed by 4 mg/min IV infusion up to 120 min	4PCC 50 units/kg
Rivaroxaban >10 mg or unknown dose	If <8 hours since last dose or unknown time, andexanet alfa 800 mg IV bolus at rate of 30 mg/min, followed by 8 mg/min IV infusion up to 120 min If ≥8 hours since last dose, andexanet alfa 400 mg IV bolus at rate of 30 mg/min, followed by 4 mg/min IV infusion up to 120 min	4PCC 50 units/kg
Apixaban ≤5 mg	Andexanet alfa 400 mg IV bolus at rate of 30 mg/min, followed by 4 mg/min IV infusion up to 120 min	4PCC 50 units/kg
Apixaban >5 mg or unknown dose	If <8 hours since last dose or unknown time, andexanet alfa 800 mg IV bolus at rate of 30 mg/min, followed by 8 mg/min IV infusion up to 120 min If ≥8 hours since last dose, andexanet alfa 400 mg IV bolus at rate of 30 mg/min, followed by 4 mg/min IV infusion up to 120 min	4PCC 50 units/kg
Edoxaban	Andexanet alfa not studied	4PCC 50 units/kg

FFP, fresh frozen plasma; IV, intravenous; 4PCC, 4-factor prothrombin complex concentrate; INR, international normalized ratio.

EVALUATION OF THERAPEUTIC OUTCOMES

- Monitor patients with acute stroke intensely for development of neurologic worsening (recurrence or extension of stroke), complications (venous thromboembolism, infection), and adverse treatment effects.
- The most common reasons for clinical deterioration in stroke patients include: (1) extension of the original lesion in the brain; (2) development of

cerebral edema and raised intracranial pressure; (3) hypertensive emergency; (4) infection (eg, urinary and respiratory tract); (5) venous thromboembolism; (6) electrolyte abnormalities and rhythm disturbances; and (7) recurrent stroke.

- For patients receiving alteplase therapy, monitor for bleeding with neurologic examination and BP every 15 minutes for 1 hour, then every half-hour for 6 hours, then every hour for 17 hours, then once every shift thereafter.
- For aspirin, clopidogrel, extended-release dipyridamole plus aspirin, warfarin, and other oral anticoagulants, monitor for bleeding daily.
- For patients receiving warfarin, check the PT/INR and hemoglobin/hematocrit daily.

See Chapter 38, Stroke, authored by Melody Ryan and Melisa Nestor, for a more detailed discussion of this topic.