H CONT. syndrome due to drug extravasation). However, both fosphenytoin and phenytoin can cause acute bradycardia and hypotension. Alternative second-line therapies include IV valproic acid (especially in generalized epilepsy) or IV levetiracetam. There is not enough evidence to support the use of lacosamide as a standard treatment in CSE.

Simultaneously with treatment, emergent evaluation for the cause of CSE should be underway, including provoking factors and triggers. A complete blood count, comprehensive metabolic profile, and evaluation for infection (with urinalysis, chest radiography, and lumbar puncture) should be considered. Head CT is usually indicated before lumbar puncture, but no test should delay the administration of antibiotics if meningitis is suspected.

If convulsions stop but the patient does not either improve within 10 minutes or return to baseline within 30 minutes, immediate continuous EEG is required to diagnose NCSE. NCSE after CSE is still a medical emergency and should be treated aggressively. If convulsive seizure activity does not cease, intubation is typically required, and third-line therapy with IV anesthesia should be initiated. IV anesthesia carries considerable risk, including prolonged ICU hospitalization and associated morbidity (infection, deep venous thrombosis) because patients are typically placed in a drug-induced coma for 24 to 48 hours. Therefore, concomitant continuous EEG monitoring is mandatory. Infusion of propofol, midazolam, or pentobarbital may be considered for NCSE that follows CSE. Hypotension is most common with pentobarbital, which may accumulate in tissues and require many days for clearance. Midazolam is least likely to cause hypotension but often leads to tolerance and tachyphylaxis. Because risk is determined by dose and duration of drug therapy, treatment should be limited to less than 48 hours. H

KEY POINTS

- **In patients with likely convulsive status epilepticus (CSE), empiric therapy is indicated without awaiting results of electroencephalography, imaging, serum studies, or lumbar puncture because a longer duration of CSE is strongly linked to worse outcomes.**
- **First-line treatment of convulsive status epilepticus is intravenous benzodiazepines typically followed by an intravenous antiepileptic drug to avoid seizure recurrence when the initial treatment wears off.**

H Nonconvulsive Status Epilepticus

NCSE refers to episodes of electrical seizure activity without clinically evident seizure activity. It should be suspected when a patient, particularly a critically ill patient, has altered mental status with an unclear cause. NCSE may occur in as many as 48% (more typically, 15% to 25%) of patients with encephalopathy who are in the ICU. Certain situations should prompt consideration of NCSE and immediate continuous EEG monitoring (see Table 18). Although EEG is required for diagnosis of NCSE, appropriate clinical correlation of EEG findings is necessary to confirm NCSE and guide treatment. EEG of a few hours duration typically is inadequate because many patients experience intermittent rather than continuous seizures. At least 24 hours of monitoring is recommended in noncomatose patients, and at least 48 hours is recommended in comatose patients.

NCSE that does not occur directly after GTCS or CSE may not necessarily carry as high a risk to the patient as NCSE that follows these seizure types, but evidence is lacking. Treatment is based on clinical examination and not on EEG alone. If the patient is not comatose, initiating aggressive therapy with intubation and an IV anesthetic–induced coma is usually avoided because risks may outweigh benefits. Outcome is typically based more on cause and less on severity or duration of seizures.

Absence status epilepticus is a form of NCSE that typically occurs in patients with a history of generalized epilepsy but sometimes is seen in healthy older patients. Patients with this condition have days to weeks of mild confusion, despite being able to speak and walk ("walking wounded"); EEG confirms the presence of continuous generalized spike-and-wave discharges. Prognosis is excellent because treatment with IV benzodiazepines, valproic acid, or levetiracetam will usually resolve the problem, even in patients with days or weeks of seizing. H

KEY POINTS

- **Nonconvulsive status epilepticus should be suspected when a patient, particularly a critically ill patient, has altered mental status with an unclear cause.**
- **Although electroencephalography is required for diagnosis of nonconvulsive status epilepticus (NCSE), appropriate clinical correlation of electroencephalographic findings is necessary to confirm NCSE and guide treatment.**
- **Nonconvulsive status epilepticus is diagnosed by continuous electroencephalographic monitoring; at least 24 hours of monitoring is recommended in noncomatose patients, and at least 48 hours is recommended in comatose patients.**

Stroke

Definition of Stroke H

Stroke is the leading cause of serious disability among adults and the fifth leading cause of death in the United States. Its incidence increases with each decade of life. The World Health Organization defines stroke as a disease of sudden-onset focal neurologic deficits associated with dysfunction in the brain, retina, or spinal cord due to occlusion or rupture of a cerebral or spinal artery. Ischemic stroke, which results from occlusion of an artery, is the most common type of stroke and can be further subclassified on the basis of its underlying cause. Transient ischemic attack (TIA) was formerly defined as a neurologic impairment lasting less than 24 hours but now is recognized as a transient neurologic

CONT. deficit without the presence of infarction on neuroimaging. Hemorrhagic strokes comprise a small proportion of all strokes but are associated with higher short-term mortality. Intracerebral hemorrhage (ICH) presents with focal neurologic deficits and may also include headache or impairment in consciousness. Subarachnoid hemorrhage (SAH) commonly presents with sudden onset severe headache and impairment in consciousness without focal neurologic deficits. Although their clinical manifestations often overlap with stroke, subdural and epidural hematomas are not considered to be strokes and are discussed in Head Injury. Determining the exact subtype of stroke a patient experiences has important implications for acute therapeutics, prevention strategies, and prognosis.

KEY POINT

- Determining the exact subtype of stroke (ischemic or hemorrhagic) has important implications for acute therapeutics, prevention strategies, and prognosis.

Diagnosis of Stroke

Stroke is a clinical diagnosis supported by neuroimaging. The clinical manifestations of stroke are highly variable. Although most strokes commonly manifest as rapid onset of specific neurologic symptoms, such as weakness, aphasia, dysphagia, and sensory changes, stroke also may present with more nonspecific symptoms, such as dizziness, altered mental status, or sudden unexplained coma. Examination will often show focal neurologic deficits. In the acute setting, rapid assessment is required to inform treatment, and validated scales, such as the National Institutes of Health Stroke Scale (NIHSS), are commonly used (**Table 23**). The neurologic examination, however, is not reliable enough to distinguish ischemic from hemorrhagic stroke, and neuroimaging is required before initiation of treatment. Noncontrast head CT is the most widely used test, given its rapid acquisition, low cost, wide availability, and high sensitivity for diagnosing hemorrhagic stroke (**Figure 10**). In ischemic stroke, the initial

TABLE 23. National Institutes of Health Stroke Scale

Parameter (Testing Method)	Scores[a]
1a. Level of consciousness	0 = normal 1 = not alert but arousable by minor stimulation 2 = not alert and requires constant verbal or painful stimuli to remain interactive 3 = unresponsive or responds with only reflexive movements
1b. Level of consciousness questions (state month and age)	0 = answers both correctly 1 = answers one correctly 2 = answers neither correctly
1c. Level of consciousness commands (close and open eyes; make fist or close one hand)	0 = performs both tasks correctly 1 = performs one task correctly 2 = performs neither task correctly
2. Best gaze (track a finger in a horizontal plane)	0 = normal 1 = partial gaze palsy or isolated cranial nerve paresis 2 = forced gaze deviation or total gaze paresis
3. Visual fields (each eye tested individually)	0 = no visual loss 1 = partial hemianopia 2 = complete hemianopia 3 = bilateral hemianopia
4. Facial palsy (show teeth, raise eyebrows, close eyes)	0 = normal 1 = minor paralysis (flattening of the nasolabial fold or asymmetry on smiling) 2 = partial paralysis (paralysis of the lower face only) 3 = complete paralysis (upper and lower face)
5. Arm strength (hold arm with palms down or lift arm for 10 s; each arm scored separately)	0 = no drift 1 = some drift but does not hit bed 2 = drifts down to bed 3 = no effort against gravity 4 = no movement
6. Leg strength (hold leg at 30 degrees for 5 s; each leg scored separately)	0 = no drift 1 = some drift but does not hit bed 2 = drifts down to bed 3 = no effort against gravity 4 = no movement

(Continued on the next page)

TABLE 23. National Institutes of Health Stroke Scale *(Continued)*

Parameter (Testing Method)	Scores[a]
7. Limb ataxia (finger-nose-finger test, heel-knee-shin slide)	0 = absent 1 = present in one limb 2 = present in two limbs
8. Sensation (pinch/pinprick tested in face, arm, and leg)	0 = normal 1 = mild to moderate sensory loss or loss of sensation in only one limb 2 = complete sensory loss
9. Best language (describe a picture, name six objects, and read five sentences)	0 = no aphasia 1 = mild to moderate aphasia (difficulty with fluency and comprehension; meaning can be identified) 2 = severe aphasia (fragmentary language, meaning cannot be clearly identified) 3 = global aphasia or mute
10. Dysarthria (repeat or read words)	0 = normal 1 = mild to moderate 2 = severe (speech not understandable)
11. Extinction/inattention (visual and tactile stimuli applied on right and left sides)	0 = normal 1 = visual or tactile extinction or mild hemispatial neglect 2 = profound hemi-inattention or extinction to more than one modality

[a]Score interpretation (based on total score): 0 = no stoke; 1-4 = minor stroke; 5-15 = moderate stroke; 16-20 = moderate to severe stroke; 21-42 = severe stroke (maximum score, 42).

Adapted from www.ninds.nih.gov/sites/default/files/NIH_Stroke_Scale_Booklet.pdf. Accessed January 17, 2018.

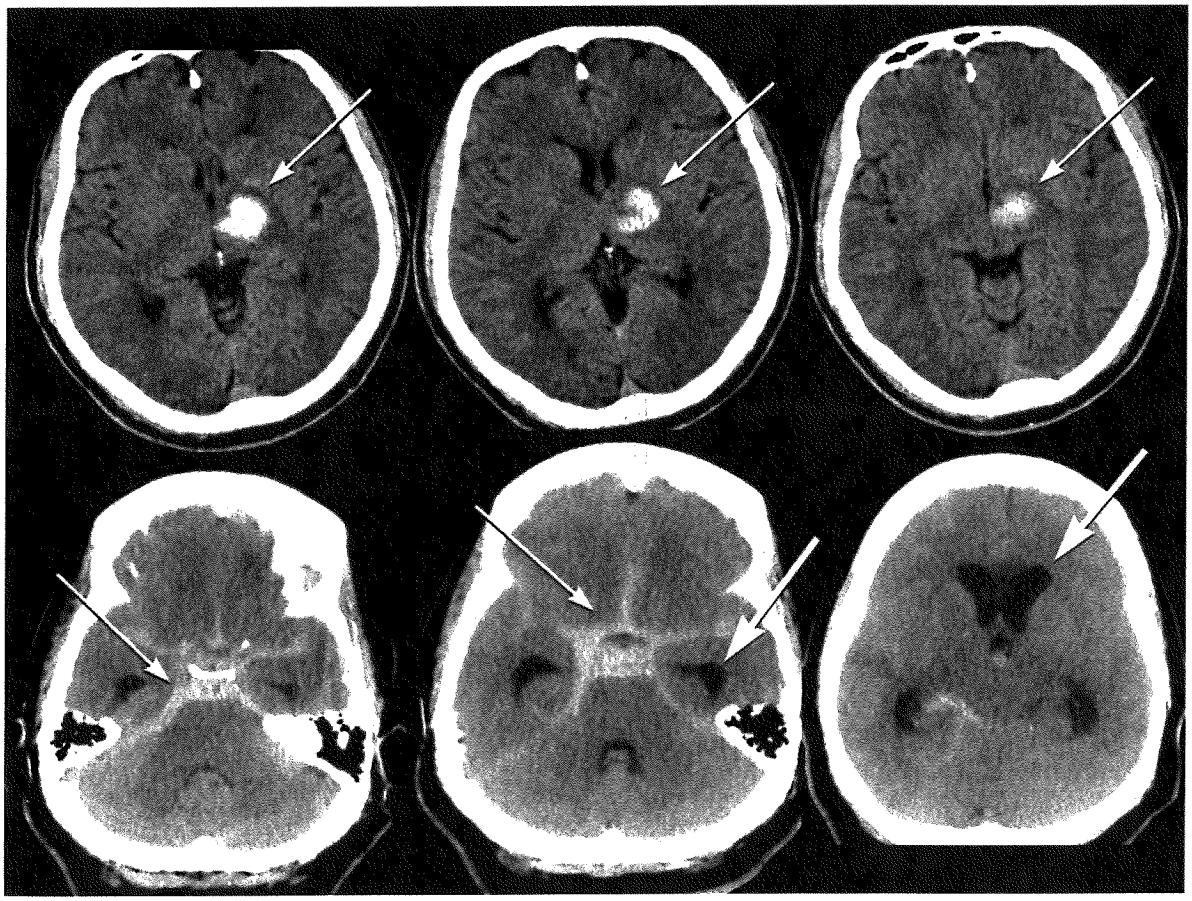

FIGURE 10. Noncontrast CT scans of the head. *Top panel*, an acute left thalamic intracerebral hemorrhage (*arrows*) without hydrocephalus or intraventricular extension is shown. *Bottom panel*, an acute subarachnoid hemorrhage is shown that involves the basal cisterns (*thinner arrows*) with associated enlargement of the lateral horn of the lateral ventricles, consistent with obstructive hydrocephalus and elevated intracranial pressure (*thicker arrows*).

H CONT.

noncontrast head CT scan is often normal, especially in patients seen within 3 hours of symptom onset (although some patients with larger deficits can exhibit early findings) (**Figure 11**). Even 24 hours after onset, a noncontrast head CT scan may not show evidence of infarction, given the poor resolution of small infarcts and those located in the brainstem. CT of the head with contrast rarely is indicated in the initial evaluation of a patient with stroke. CT angiography (CTA) of the head and neck, however, may be performed acutely if endovascular therapy is considered or in otherwise unexplained acute coma to rule out basilar artery thrombosis.

MRI is more sensitive than CT for acute infarction, with changes on the diffusion-weighted imaging sequence apparent within minutes from onset (**Figure 12**). The advantages of MRI include the ability to visualize small strokes, multifocal or bilateral infarcts that may suggest an embolic cause, and the presence of microbleeding. MRI, however, is never the initial test of choice in acute suspected stroke because of its longer acquisition time; if indicated, it is obtained after the initial noncontrast head CT.

Among patients with ICH seen on a noncontrast head CT scan, MRI or CTA is considered if clinical factors are present that raise the suspicion of a cause of hemorrhage other than hypertension or amyloid angiopathy, such as arteriovenous malformation. Likewise, if a patient has symptoms suggestive of SAH and noncontrast head CT findings are normal, lumbar puncture is required to evaluate for the presence of blood or xanthochromia (yellow color stemming from erythrocyte breakdown). If SAH is confirmed,

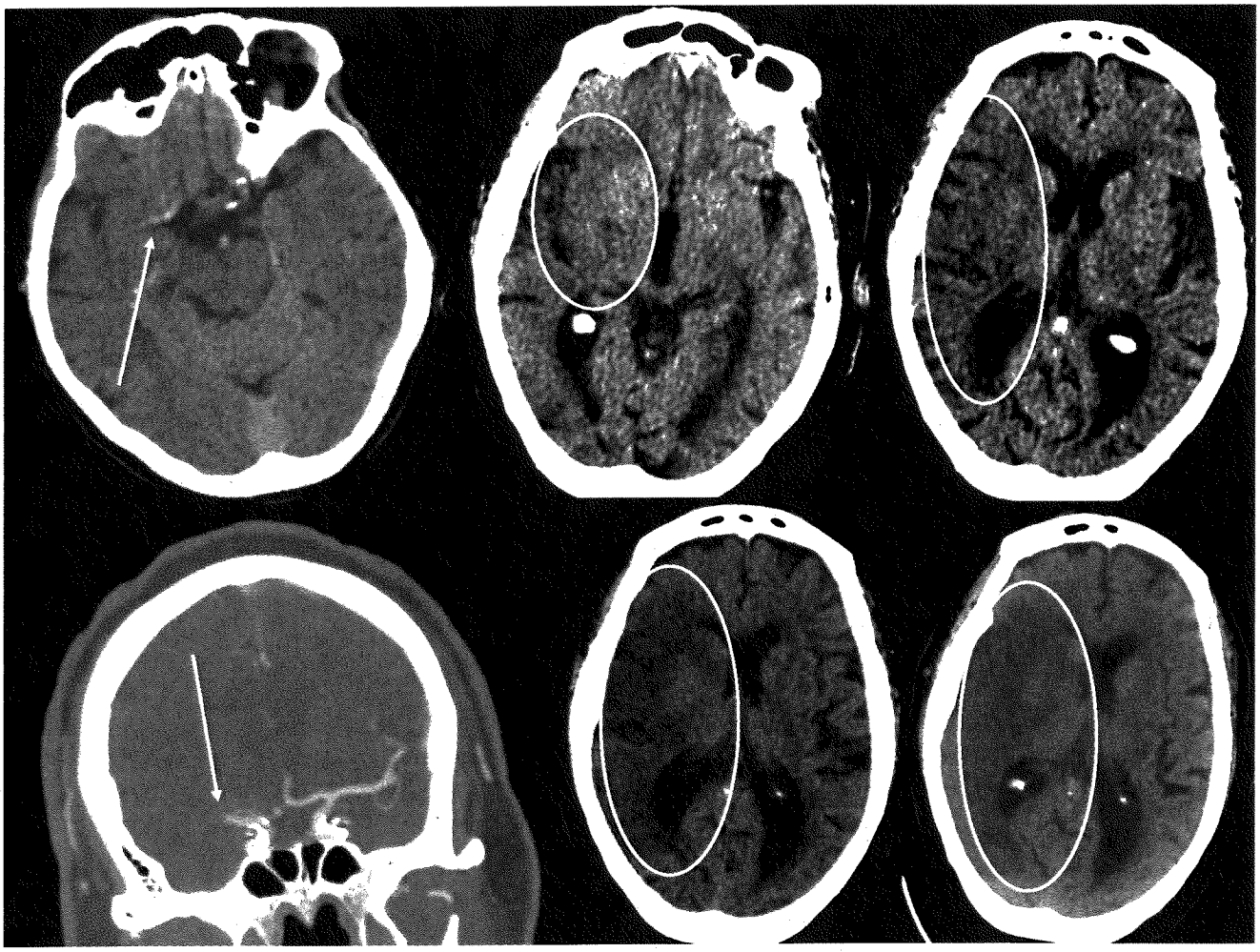

FIGURE 11. Imaging findings in acute ischemic stroke. *Top left panel,* CT scan of the head without contrast obtained 4 hours after acute onset of left-sided weakness and hemiparesis. The *arrow* points to a dense middle cerebral artery sign suggestive of a thrombus. *Top middle panel,* CT scan of the head showing hypodensity in the right insula (*oval*). *Top right panel,* CT scan of the head from the same patient showing early loss of the gray-white matter differentiation in the right middle cerebral artery territory distribution (*oval*). *Bottom left panel,* CT angiogram of the head showing abrupt cessation of filling in the right middle cerebral artery *(arrow*). *Bottom middle and right panels,* CT scans of the head from the same patient as above 36 hours after symptom onset showing more prominent hypodensity (*middle panel, oval*) and cerebral edema (*right panel, oval*).

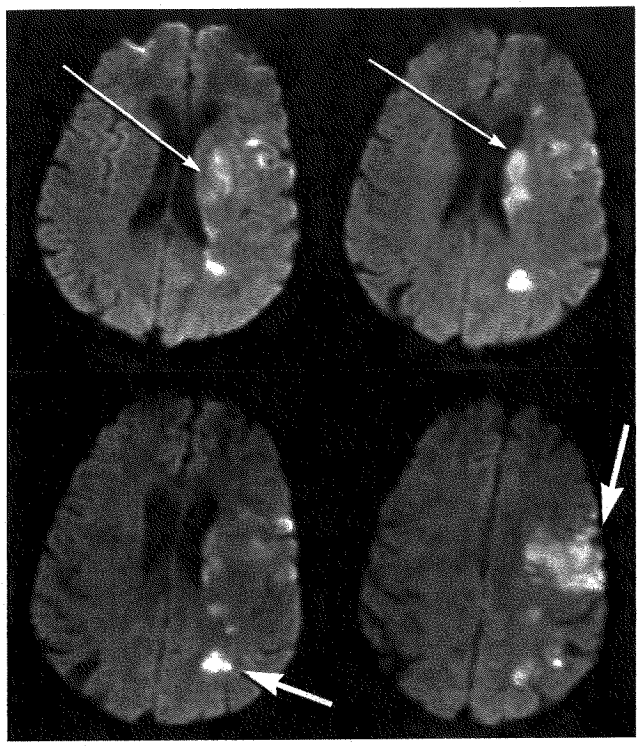

FIGURE 12. Diffusion-weighted MRIs from a patient with symptomatic atherosclerosis of the left middle cerebral artery reveal an acute infarction in deep (*thinner arrows*) and superficial (*thicker arrows*) structures in the left cerebral hemisphere.

CONT. catheter-based angiography is required to diagnose, and potentially treat, a cerebral aneurysm.

Results of the physical and neurologic examination most likely will suggest the cause of ischemic stroke, such as the presence of atrial fibrillation or a carotid bruit. Further evaluation with cardiac testing or vessel imaging is required to confirm these causes.

KEY POINTS

- Neuroimaging, preferably noncontrast head CT, is required before initiating treatment for stroke.
- Although MRI is more sensitive than CT for diagnosing acute infraction, it is not the initial test of choice to exclude hemorrhagic stroke or to make treatment decisions about thrombolysis for ischemic stroke because of its longer acquisition time.

Stroke Subtypes

Transient Ischemic Attack

TIA is characterized by a temporary focal neurologic deficit with an absence of infarction on neurologic imaging. Similar to those of acute ischemic stroke, symptoms of TIA include hemiparesis, mono-ocular or visual field loss, dysarthria, aphasia, and sensory loss. The presence of paresthesia, isolated dizziness or vertigo, or memory loss is more consistent with migraine or seizure. Patients with TIA are at high risk of stroke within the first 48 hours after symptom onset and should be evaluated promptly.

Several post-TIA stroke prediction scoring systems have been developed, with the most widely used being the ABCD[2] score, which is based on Age, Blood pressure, Clinical presentation, Duration of symptoms, and the presence of Diabetes mellitus (**Table 24**). TIA scoring systems, however, do not identify with sufficient sensitivity the highest-risk patients for whom treatment can ameliorate the risk of stroke. Patients with high-grade extracranial internal carotid artery (ICA) stenosis who have a TIA in a downstream neurologic territory have the greatest short-term risk of stroke. This risk is highest within 2 weeks of TIA for those with greater than 70% stenosis, although 50% to 70% stenosis also carries significant associated risk. In the long term, the risk of stroke is high among patients with atrial fibrillation or other cardioembolic sources requiring anticoagulation.

Expedited vascular imaging of the ICA and cardiac evaluation for atrial fibrillation are required for all patients with TIA. The initial test of choice for evaluating ICA stenosis is duplex ultrasonography because of its wide availability, low cost, and low risk; if high-grade ICA stenosis is detected and the patient is a candidate for surgery or stenting, confirmatory testing is required before intervention. Cardiac evaluation should include electrocardiography for atrial fibrillation, which may be followed by longer-term monitoring. Echocardiography is performed if there is a clinical suspicion of a cardioembolic source or structural heart disease.

TABLE 24. ABCD Score[a]

Patient Characteristics	Score[b]
Age ≥60 y	1
Blood pressure ≥140/90 mm Hg	1
Clinical symptoms	
Focal weakness with the TIA	2
Speech impairment without weakness	1
Duration of TIA	
≥60 min	2
10-59 min	1
Diabetes mellitus present	1

TIA = transient ischemic attack.

[a]Based on Age, Blood pressure, Clinical presentation, Duration of symptoms, and the presence of Diabetes mellitus.

[b]The 48-hour stroke risk based on total score: 0-1 = 0%; 2-3 = 1.3%; 4-5 = 4.1%; 6-7 = 8.1%.

Data from Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet. 2007;369:283-92. [PMID: 17258668]

KEY POINTS

- Patients with a greater than 70% extracranial stenosis of the internal carotid artery who have a transient ischemic attack in a downstream neurologic territory have the highest risk of stroke within 2 weeks.
- Expedited vascular imaging of the internal carotid artery and cardiac evaluation for atrial fibrillation are required for all patients with transient ischemic attack.

Ischemic Stroke

Large Artery Atherosclerosis

The main mechanism of stroke due to large-artery atherosclerosis is plaque rupture with artery-to-artery embolism. The extracranial carotid artery is frequently involved; the intracranial arteries most commonly affected are the intracranial ICA, middle cerebral arteries, vertebral-basilar arterial junction, and midbasilar artery. Patients with stenoses of the extracranial ICA and the intracranial arteries are at high short-term risk for recurrent stroke and require prompt evaluation. As with TIAs, the extracranial carotid arteries are best evaluated with duplex ultrasonography. Magnetic resonance angiography (MRA) and CTA are both appropriate confirmatory tests after ultrasonography to inform intervention or if duplex examination is not available (**Figure 13**). Transcranial Doppler ultrasonography may help diagnose large-vessel intracranial atherosclerosis, although MRA and CTA are more sensitive tests and can help confirm the diagnosis. Catheter-based angiography is rarely used to diagnose either extracranial or intracranial vessel disease and is associated with a small risk of stroke.

Cardioembolic Stroke

A cardioembolic cause is suggested by clinical and radiologic factors, including infarcts that occur in multiple arterial territories or are located near the cortical surface of the brain with normal arterial imaging. Atrial fibrillation is the most common cardioembolic cause of stroke. Other potential

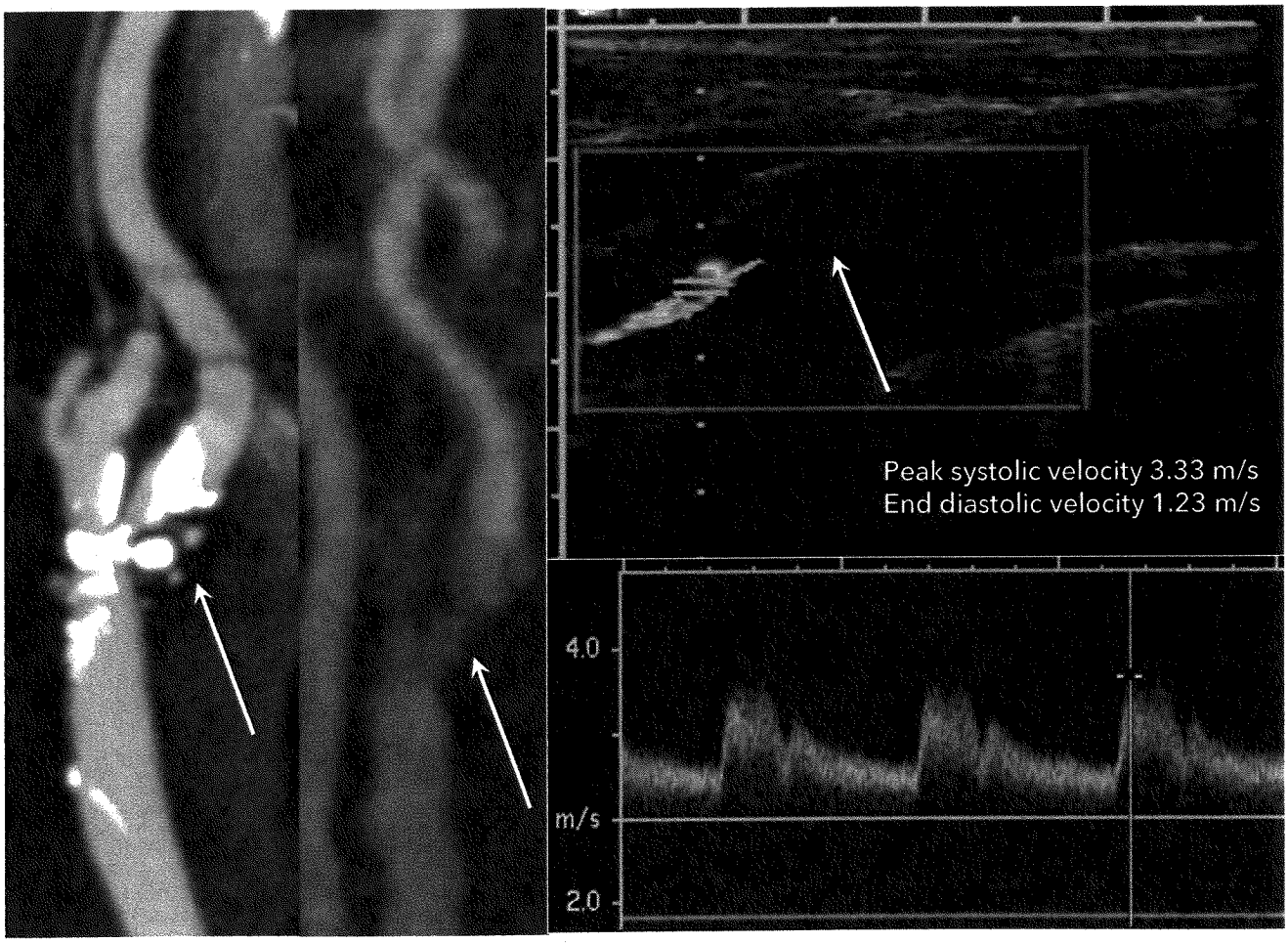

FIGURE 13. Diagnostic imaging modalities in a patient with a symptomatic extracranial internal carotid artery atherosclerotic plaque and associated 90% stenosis. The CT angiogram (*left panel*) and magnetic resonance angiogram (*middle panel*) show high grade stenosis at the origin of the internal carotid artery (*arrows*). Carotid ultrasounds (*right panel*) of the extracranial proximal internal carotid artery show a large plaque at the origin (*arrow*) of the artery, with associated elevated systolic (3.33 m/s) and diastolic (1.23 m/s) velocities consistent with 80% to 99% stenosis.

H CONT. cardioembolic sources include new ventricular thrombus after myocardial infarction and severe valvular disease (for example, rheumatic disease, infective endocarditis, and bioprosthetic and mechanical heart valves).

Radiographic findings suggestive of a cardioembolic source, however, are insufficient grounds for initiating anticoagulation. Patients admitted to the hospital with ischemic stroke should have telemetry monitoring to assess for atrial fibrillation. Similarly, when a clinical suspicion of structural heart disease or embolic stroke exists, transthoracic echocardiography is indicated to evaluate for a cardiac source that may require anticoagulation. Echocardiography also may reveal other findings suggesting the cause of stroke, such as a reduced ejection fraction or patent foramen ovale (PFO), although anticoagulation is not routinely indicated for patients with these conditions. The use of transesophageal echocardiography to evaluate for an intracardiac source of stroke is not routinely indicated, given the low yield for findings that require anticoagulation or surgery. In younger patients without stroke risk factors or in whom suspicion of endocarditis or an intracardiac tumor (such as myxoma or fibroelastoma) exists, transesophageal echocardiography may be considered on a case-by-case basis. For further details on anticoagulation criteria, see MKSAP 18 Cardiovascular Disease.

Small Subcortical Infarcts (Lacunar Infarcts)

Lacunar infarcts commonly lead to isolated motor or sensory syndromes; they rarely affect cognition or mental status. These infarcts (which are < 1.5 cm in diameter) involve the deep white matter, basal ganglia, or brainstem. Pathologically, these infarcts are due to occlusion of small penetrating arteries arising from ICAs (most commonly the middle cerebral and basilar arteries). The main risk factor is hypertension, which leads to local damage at the level of the penetrating artery with subsequent occlusion. Other stroke sources include artery-to-artery embolic thrombi from more proximal sources. Patients with lacunar infarcts still require vessel imaging of the extracranial ICAs to inform secondary prevention.

Cryptogenic Causes of Stroke

In many patients with ischemic stroke, a clear cause is not apparent: there is no lacunar infarct, arterial imaging is normal, and no clear cardioembolic source of stroke (such as atrial fibrillation) is found. When this occurs, the patient's clinical syndrome, underlying medical comorbidities, and neuroimaging characteristics can inform which additional diagnostic testing should be considered.

In a younger patient without risk factors for cardiovascular disease, an evaluation for autoimmune and hypercoagulable disorders should be considered, particularly with nonneurologic systemic findings. Hypercoagulable disorders, PFO, and other rare cardioembolic causes may present with an infarct pattern similar to that of atrial fibrillation. A PFO with a right-to-left shunt (diagnosed with a bubble study on transthoracic echocardiography) may explain stroke in a younger patient but is associated with a low risk of recurrent stroke. For further information, including recent recommendations regarding percutaneous PFO closure to prevent a secondary stroke, see MKSAP 18 Cardiovascular Disease. Cerebral vasculitis is an extremely rare cause of stroke and presents with numerous infarcts affecting multiple arterial distributions.

Many patients with cryptogenic stroke may have undiagnosed paroxysmal atrial fibrillation. Neuroimaging findings are similar to those of atrial fibrillation without abnormalities on telemetry or electrocardiography. Prolonged cardiac monitoring with either surface electrodes or an implantable monitor can reveal paroxysmal atrial fibrillation in approximately one third of these patients. In patients with an implantable pacemaker, interrogation of the device may also reveal episodes consistent with atrial fibrillation. The benefit of anticoagulation for stroke prevention if atrial fibrillation is not found on monitoring is unclear. H

KEY POINTS

- Carotid and transcranial Doppler ultrasonography may help diagnose large vessel atherosclerosis in a patient with ischemic stroke, although magnetic resonance angiography and CT angiography may provide additional information; catheter-based angiography is rarely used to diagnose either extracranial or intracranial vessel disease and is associated with a small risk of stroke.
- Atrial fibrillation is the most common cardioembolic cause of stroke, and anticoagulation is indicated; radiographic findings suggestive of a cardioembolic source, however, are insufficient grounds for initiating anticoagulation.
- The use of transesophageal echocardiography to evaluate for an intracardiac source of stroke is not routinely indicated, given the low yield for findings that require anticoagulation or surgery. HVC
- Lacunar (or small subcortical) infarcts resulting in isolated motor or sensory syndromes are caused by occlusion of the small penetrating arteries arising from intracranial arteries; the main risk factor for lacunar infarcts is hypertension.
- Many patients with cryptogenic stroke may have undiagnosed paroxysmal atrial fibrillation, and prolonged cardiac monitoring should be considered.

Hemorrhagic Stroke H

Subarachnoid Hemorrhage

Examination findings suggestive of SAH include altered mental status, nuchal rigidity, pupillary dilation from compression of the oculomotor nerve (cranial nerve III) by a posterior communicating artery aneurysm, or subhyaloid hemorrhages on funduscopy. The most common cause of subarachnoid hemorrhage is saccular (berry) aneurysm rupture, with intracranial arterial dissection and mycotic aneurysm rupture occurring less commonly. Other rare causes of SAH are the reversible cerebral vasoconstriction syndromes, dural

CONT. sinus thrombosis, vascular malformations, and cerebral amyloid angiopathy. Saccular aneurysms often can be visualized with CTA or MRA, although the resolution is not sufficient to detect smaller aneurysms; catheter-based angiography is necessary for the definitive diagnosis of aneurysms and other causes of SAH.

Elevated intracranial pressure from obstructive hydrocephalus and/or global cerebral edema is a common consequence of SAH. Examination findings that raise concern for elevated intracranial pressure include impairment in consciousness, loss of brainstem reflexes, and stereotyped posturing movements to painful stimuli. The presence of hydrocephalus on neuroimaging is associated with high mortality and should prompt neurosurgical placement of an external ventricular drain to relieve (and measure) elevated intracranial pressure. Impaired consciousness due to nonconvulsive status epilepticus also may occur and requires electroencephalographic monitoring for diagnosis.

Intracerebral Hemorrhage

ICH can present similarly to ischemic stroke, with headache and impaired consciousness as distinguishing characteristics. The most common cause of ICH that affects deep structures of the brain (thalamus, basal ganglia, pons, cerebellum) is hypertension. Lobar hemorrhages near the cortical surface may have various causes, including hypertension, hemorrhagic tumors, and cortical vein thrombosis. In patients older than 55 years, especially in those without hypertension, lobar ICH may be due to cerebral amyloid angiopathy. In this syndrome, amyloid protein similar to that seen pathologically in Alzheimer disease deposits in cerebral arterioles near the cortical surface, thereby weakening the arterial wall and making it prone to rupture.

The mainstay of acute treatment and prevention is control of blood pressure. Clinical and radiologic features can be used to calculate a patient's ICH score, which informs 30-day mortality and is recommended in the assessment of patients with ICH (**Table 25**). The main cause of early neurologic deterioration is hematoma expansion. Another leading cause of death is early withdrawal of care. Guidelines caution against termination of care within the first 48 hours.

KEY POINTS

- Catheter-based angiography is necessary for the definitive diagnosis of aneurysms and other causes of subarachnoid hemorrhage.
- In subarachnoid hemorrhage, the presence of hydrocephalus on neuroimaging is associated with high mortality and should prompt neurosurgical placement of an external ventricular drain to relieve elevated intracranial pressure.
- The most common cause of intracerebral hemorrhage that affects deep structures of the brain (thalamus, basal ganglia, pons, cerebellum) is hypertension; the mainstay of prevention is control of blood pressure.

TABLE 25. Intracerebral Hemorrhage Score[a,b]

Clinical and Imaging Findings		Points
Glasgow Coma Scale score	3-4	2
	5-12	1
	13-15	0
Age	80 y or older	1
	Younger than 80 y	0
Infratentorial (brainstem, cerebellum)	Yes	1
	No	0
Volume	Greater than 30 mL	1
	Less than 30 mL	0
Intraventricular hemorrhage	Yes	1
	No	0

[a]30-Day mortality based on total score: 0 = 0%; 1 = 13%; 2 = 26%; 3 = 72%; 4 = 97%; 5 and 6 = 100%.

Adapted with permission from: Hemphill JC 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. Stroke. 2001;32:891-7. [PMID: 11283388]

In-Hospital Stroke Considerations

In-hospital stroke is most often ischemic and frequently observed perioperatively. Patients undergoing cardiac surgery involving cardiopulmonary bypass, particularly multivalve procedures, are at highest risk for stroke in the postoperative setting. The most common cause is atrial fibrillation.

The modifiable preoperative risk factors for in-hospital stroke are similar to those causing stroke in the short term without surgery, including symptomatic extracranial ICA stenosis of greater than 70%. Patients with a recent stroke secondary to ICA stenosis who are undergoing nonemergent surgery are likely to benefit from revascularization beforehand. The presence of asymptomatic ICA stenosis, however, is not clearly associated with perioperative stroke, and routine prophylactic ICA revascularization is not indicated.

Stroke within 30 days of surgery, regardless of cause, increases the risk of perioperative stroke; elective surgeries within this time period should be avoided. Patients with stroke involving a large brain volume or with a recent hemorrhagic stroke also are at risk of cerebral hemorrhage if placed on cardiopulmonary bypass and/or anticoagulation. If possible, nonemergency major cardiac procedures should be avoided.

KEY POINTS

- Patients undergoing cardiac surgery involving cardiopulmonary bypass, particularly multivalve procedures, are at highest risk for stroke in the postoperative setting, most commonly from atrial fibrillation.
- Stroke within 30 days of surgery, regardless of cause, increases the risk of perioperative stroke, and elective surgeries within this time period should be avoided.

H Acute Stroke Therapy

Ischemic Stroke Treatment

Thrombolysis and Endovascular Therapy

Intravenous recombinant tissue plasminogen activator (alteplase) is the only thrombolytic agent approved for use in acute ischemic stroke. Alteplase is most effective when administered early, and treatment within 3 hours of ischemic stroke onset with disabling symptoms is associated with a significant reduction in disability at 3 months. Although treatment within 4.5 hours also may have clinical benefit, treatment beyond 3 hours is not approved by the FDA. Because of the associated delays, obtaining advanced imaging or laboratory values should be avoided before treatment unless coagulopathy or thrombocytopenia is suspected. Treatment should start within 60 minutes of arrival at the emergency department or detection of in-hospital stroke, with best practices recommending treatment within 45 minutes. Contraindications for treatment with alteplase have evolved over the years, with the latest guidelines clarifying relative exclusion criteria and defining nondisabling symptoms (**Table 26**).

The main complication of alteplase treatment is symptomatic ICH, which can present with headache or worsening of NIHSS score or level of consciousness. Symptomatic hemorrhage occurs in up to 6% of treated patients, and mortality can be as high as 50% when present. The main risk factors for symptomatic hemorrhage are treatment after 4.5 hours and hypertension before and after treatment. Accordingly, before treatment with alteplase, the patient's blood pressure should be less than 185/110 mm Hg. Higher readings should prompt administration of intravenous labetalol or nicardipine before alteplase. Nitrates should be avoided because of their potential to increase intracranial pressure.

After treatment with alteplase, frequent monitoring of neurologic status and vital signs is required in the first 24 hours. Neurologic worsening should prompt urgent neuroimaging. Blood pressure should be maintained below 180/105 mm Hg, and both antiplatelet and anticoagulant agents should be held for the first 24 hours after alteplase administration. After 24 hours, antiplatelet agents for stroke prevention and anticoagulant agents for deep venous thrombosis prevention can be started if hemorrhage is absent on imaging.

Endovascular therapy (primarily with intra-arterial mechanical thrombectomy) within 24 hours of stroke onset can be considered for select patients with a clinically suspected large-vessel occlusion and specific examination and radiologic findings, such as a measurable neurologic deficit and small but radiographically evident ischemic changes. In patients for whom endovascular therapy is considered, prompt noninvasive vessel imaging with CT or MRA is recommended. The evaluation for endovascular stroke therapy with vessel imaging, however, should not replace or delay the administration of

TABLE 26. Contraindications to Intravenous Alteplase in Adults With Acute Ischemic Stroke

Absolute Exclusion Criteria	Relative Exclusion Criteria
Significant head trauma or prior stroke in the previous 3 months	Minor or rapidly improving nondisabling symptoms[a]
Suspicion of subarachnoid hemorrhage	Pregnancy
Noncompressible site arterial puncture within 7 days	Seizure at onset
Intracranial neoplasm, arteriovenous malformation, aneurysm	Major surgery or serious trauma within 14 days
Recent intracranial or spinal surgery	Recent gastrointestinal or genitourinary bleeding within 21 days
Blood pressure ≥185/110 mmHg despite treatment	Recent acute myocardial infarction
Active internal bleeding	
Active bleeding diathesis	
Platelet count <100,000/μL (100 × 10^9/L)	
Heparin within 48 hours with an activated partial thromboplastin time above normal range	
Current use of anticoagulant with INR >1.7	
Current use of non-vitamin K antagonist anticoagulants (within 48 hours) with associated elevated relevant laboratory tests	
Blood glucose less 50 mg/dL (2.8 mmol/L)	
Noncontrast head CT demonstrated multi-lobar infarction with >1/3 of the hemisphere involved	

[a]Disabling symptoms are defined as complete hemianopia (score of 2-3 on National Institutes of Health Stroke Scale [NIHSS] question 3), visual or sensory extinction (score of 1-2 on NIHSS question 11), any weakness against gravity (score of 2-4 on NIHSS question 6 or 7), and total NIHSS score >5.

Adapted with permission from: Demaerschalk BM, Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, Grotta JC, et al; American Heart Association Stroke Council and Council on Epidemiology and Prevention. Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2016;47:581-641. [PMID: 26696642] doi:10.1161/STR.0000000000000086

CONT. alteplase in otherwise eligible patients. A treatment algorithm for stroke within 6 hours of onset is provided in **Figure 14**.

Antiplatelet Therapy, Anticoagulation, and Medical Management

For the many patients with acute ischemic stroke who are not eligible for thrombolysis or endovascular stroke therapy, antiplatelet therapy is the mainstay of acute treatment. When administered either orally or rectally within 48 hours of stoke, aspirin reduces the short-term risk of recurrent stroke, and its use in the acute setting is a stroke-specific quality-of-care core measure. Monotherapy with clopidogrel, however, has no established benefit in the acute stroke setting.

The patient with TIA or minor stroke, usually defined as an NIHSS score of 5 or less, has been the focus of recent trials of antiplatelet therapy because of the high short-term risk of recurrent events. In one recent trial, aspirin was compared to ticagrelor within 24 hours of stroke onset, and no difference between the two medications in the risk of recurrent stroke during 90 days of treatment was noted. Another study compared aspirin monotherapy for 90 days with aspirin and clopidogrel combined for 21 days followed by clopidogrel monotherapy as long as 69 days. The combination arm had a 3% absolute reduction in recurrent ischemic stroke at 90 days, with no difference in hemorrhagic stroke. Further clinical trials are ongoing to evaluate the safety and efficacy of dual antiplatelet agents in the settings of acute minor stroke and TIA.

Acute administration of anticoagulation in ischemic strokes (whether related to atrial fibrillation or not) does not reduce the short-term risk of recurrent stroke and increases the risk of hemorrhage into the territory of cerebral infarction (hemorrhagic conversion).

Management of acute hypertension in ischemic stroke differs when thrombolysis is not involved. Blood pressure should not be treated within the first 48 hours unless it is greater than 220/120 mm Hg or there is evidence of end-organ dysfunction. Acute antihypertensive therapy has been associated with neurologic worsening in patients with ischemic stroke and should be started slowly after the first 48 hours until secondary prevention targets are reached. Statins have not been shown to reduce the risk of recurrent stroke when administered within 30 days but can be considered after a dysphagia evaluation has been completed, especially in those patients with an atherosclerotic stroke subtype. See Dyslipidemia section in MKSAP 18 General Internal Medicine.

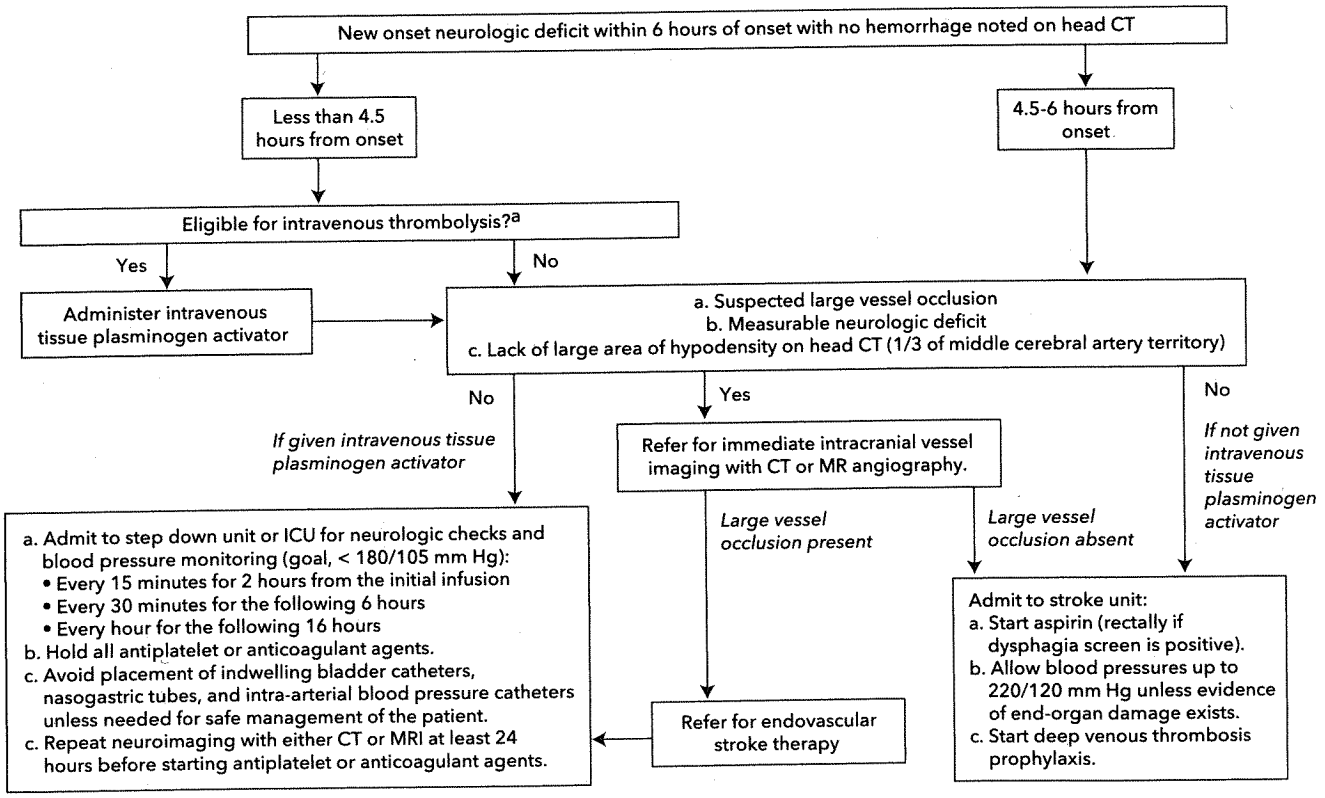

FIGURE 14. Proposed pathway for the evaluation and treatment of an acute stroke within 6 hours of onset.

[a]See Table 26 for exclusion criteria for alteplase (tissue plasminogen activator).

KEY POINTS

- Treatment with intravenous recombinant tissue plasminogen activator (alteplase) within 3 hours of ischemic stroke onset is associated with a significant reduction in disability at 3 months after stroke; treatment within 4.5 hours of onset also may have clinical benefit but is not FDA approved.
- Endovascular therapy within 24 hours of stroke onset can be considered for select patients with a clinically suspected large-vessel occlusion and specific examination and radiologic findings, such as a measurable neurologic deficit and small but radiographically evident ischemic changes.
- When administered within 48 hours of ischemic stroke that is not eligible for thrombolysis, aspirin reduces the short-term risk of recurrent stroke; its use in the acute setting is a stroke-specific quality-of-care core measure.
- Acute administration of anticoagulation for ischemic stroke (whether related to atrial fibrillation or not) does not reduce the short-term risk of recurrent stroke and increases the risk of hemorrhage into the territory of cerebral infarction (hemorrhagic conversion).

Hemorrhagic Stroke Treatment

CONT.

Intracerebral Hemorrhage Treatment

Treatment of acute ICH is centered on preventing hematoma expansion. The primary predictor of early hematoma expansion is elevated blood pressure. Treatment of blood pressure is recommended for patients with ICH who have a systolic blood pressure greater than 180 mm Hg, although the most appropriate agent for the blood pressure control in this circumstance is not well established. Parenteral medications delivered by intravenous infusion with frequent blood pressure monitoring have the benefit of close titration to the intended target. Intravenous nitrates (such as nitroglycerin) and nitroprusside may raise intracranial pressure and reduce blood flow to the ischemic region and should be avoided in patients with ICH. Guidelines for the treatment of ICH indicate that acutely treating the systolic blood pressure in a specialized intensive care unit until it is 140 mm Hg is reasonable if the presenting systolic pressure is 150 to 220 mm Hg.

A recently completed trial compared a goal systolic blood pressure of 110 to 140 mm Hg with one of 140 to 180 mm Hg in patients with a systolic blood pressure of greater than 180 mm Hg who were seen within 4.5 hours of ICH onset. The more intensive control arm achieved a mean systolic blood pressure of 128 mm Hg versus 141 mm Hg in the usual care arm. No difference in mortality or neurologic outcomes was seen, but a significantly higher rate of adverse renal events occurred with intensive control. Treating systolic blood pressure if greater than 180 mm Hg is still advised but should be performed cautiously, and systolic blood pressure goals of less 140 mm Hg should be avoided.

Another risk factor for hematoma expansion is coagulopathy due to either antiplatelet agent use or anticoagulation. The use of platelet transfusion has been specifically studied in ICH in the setting of antiplatelet agent use, and no clinical benefit has been shown. Guidelines advise against its routine use. Anticoagulation should be reversed, although this incurs an increased risk of thrombotic events. For patients without coagulopathy, recombinant factor VII has no neurologic benefit and is associated with high rates of venous thromboembolic events.

Another source of neurologic decline in patients with ICH is nonconvulsive status epilepticus, which may present with impaired consciousness. Use of prophylactic antiepileptic medications in patients with ICH is not recommended, however, unless there are definitive clinical or electroencephalographic seizures.

Elevated intracranial pressure is a major determinant of morbidity and mortality in ICH. Osmotherapy with mannitol or hypertonic saline may temporarily reduce intracranial pressure in ICH; glucocorticoids are ineffective in reducing cerebral edema in ICH and should not be routinely administered. External ventricular drainage is indicated with hydrocephalus and impaired consciousness; other surgical measures are not routinely indicated unless as life-saving measures in rapidly deteriorating patients. Cerebellar hemorrhages greater than 3 centimeters in diameter are the exception because early surgical evacuation is necessary to prevent hydrocephalus, brainstem compression, and neurologic deterioration.

KEY POINTS

- Treatment of blood pressure is recommended for patients with intracerebral hemorrhage whose systolic blood pressure is greater than 180 mm Hg; intravenous nitrates should be avoided.
- Routine use of platelet transfusion in patients with intracerebral hemorrhage who are being treated with antiplatelet agents is not indicated. **HVC**
- Osmotherapy with mannitol or hypertonic saline may temporarily reduce intracranial pressure in patients with intracerebral hemorrhage; glucocorticoids are ineffective and should not be routinely administered.
- In patients with intracerebral hemorrhage, early surgical evacuation of cerebellar hemorrhages greater than 3 cm in diameter is necessary to prevent hydrocephalus, brainstem compression, and neurologic deterioration.

Subarachnoid Hemorrhage Treatment

Treatment of SAH focuses on prevention of early (≤48 hours) and late neurologic complications. Within the first 48 hours, a major cause of morbidity is aneurysmal rebleeding; early surgical exclusion of the ruptured aneurysm and maintenance of a blood pressure of less than 140/80 mm Hg is required. Elevated intracranial pressure from obstructive hydrocephalus, cerebral edema, seizures, and cerebral vasospasm are other leading causes of poor outcomes.

H CONT.

Cerebral vasospasm with resultant cerebral ischemia and neurologic worsening may develop beginning near day 5. The degree of hemorrhage on a head CT may predict the risk of vasospasm, but frequent monitoring and daily transcranial Doppler imaging is recommended in all patients. Nimodipine should be started as early as possible to improve neurologic outcomes. The drug is continued for 21 days or until hospital discharge. If there is a high clinical suspicion of vasospasm, CTA or catheter-based angiography may be needed to establish vasospasm as the cause of neurologic worsening. The latter has the added benefit of potential endovascular treatment, including use of intra-arterial vasodilators and angioplasty. Another treatment option for vasospasm in patients with a treated aneurysm is induced hypertension, although the exact treatment targets are not well established.

Medical complications are a significant source of morbidity and mortality in patients with SAH. Patients with impaired consciousness and coma at presentation are at highest risk for stunned myocardium (with a decrease in left ventricular ejection fraction) and pulmonary edema due to the large sympathetic surge in SAH. Other medical complications include pulmonary and urinary tract infections, dysphagia, the syndrome of inappropriate antidiuretic hormone secretion, and cerebral salt wasting. Because of these possible medical and neurologic complications, patients with SAH require care in a specialized ICU with experience in treating SAH. H

KEY POINTS

- Within the first 48 hours of a subarachnoid hemorrhage, aneurysmal rebleeding is a major cause of morbidity; early surgical exclusion of the ruptured aneurysm and maintaining a blood pressure of less than 140/80 mm Hg is required.
- In aneurysmal subarachnoid hemorrhage, cerebral vasospasm with resultant cerebral ischemia and neurologic worsening may develop beginning near day 5, and all patients should be treated with nimodipine to prevent poor neurological outcomes.

Stroke Prevention

Primary Prevention

MKSAP 18 General Internal Medicine provides information on the treatment of cardiovascular risk factors related to primary prevention of stroke. Patients with asymptomatic ICA stenosis require primary prevention strategies similar to those used for patients with asymptomatic atherosclerotic disease. Contemporary best medical therapy, including high-intensity statin therapy, is associated with a low risk of first stroke, likely less than 2% per year. ICA revascularization may reduce the risk of stroke further, but the risk of the procedure itself must be weighed against the potential benefit. ICA revascularization for primary prevention is not warranted unless high-risk stroke features are present, such as stenosis greater than 80% or rapid progression of stenosis. For patients with high-risk predictors, the decision to refer for revascularization should be made on an individual basis. Ongoing clinical trials may provide more information on the relative advantages of revascularization and medical therapy.

The main modifiable risk factors for intracranial arterial aneurysm growth and rupture are hypertension and active tobacco use. Treatment of both is indicated. Surgical treatment of aneurysms with either endovascular therapy or craniotomy is associated with sufficiently high neurologic morbidity that treatment is reserved for patients at high risk of rupture and low surgical risk. The location and size of the aneurysm are the primary determinants of rupture risk, and both MRA and CTA can show these features noninvasively. Aneurysms less than 7 millimeters in diameter in the posterior circulation and less than 12 millimeters in the anterior circulation have a low risk of rupture and can be managed conservatively. Patients with these aneurysms should undergo annual noninvasive imaging because aneurysmal growth is a risk factor for rupture and may be an indication for surgery. Patients with two or more relatives with intracranial aneurysms or SAH also should be offered screening with noninvasive neuroimaging. Other predictors of aneurysmal rupture that should prompt surgical consideration include a previous aneurysmal SAH or the presence of cranial nerve palsy.

KEY POINTS

- Routine internal carotid artery revascularization for primary prevention of stroke is not warranted unless high-risk stroke features are present, such as stenosis greater than 80% or rapid progression of stenosis. **HVC**
- Aneurysms less than 7 millimeters in diameter in the posterior circulation and less than 12 millimeters in the anterior circulation have a low risk of rupture and can be managed conservatively with annual noninvasive neuroimaging. **HVC**

Secondary Prevention

Lifestyle Modifications and Medical Management

The risk factors for a second stroke are similar to those for ischemic heart disease and other atherosclerotic disease. Patients with stroke benefit from diet and exercise changes to maintain cardiometabolic health. Patients with ICH are at high risk for recurrent stroke due to hypertension; after the acute in-hospital setting, a target blood pressure of less than 130/80 mm Hg is advised. Similarly, patients with small subcortical infarcts in whom hypertension is the primary risk factor may also benefit from a systolic blood pressure of less than 130 mm Hg. High-intensity statin therapy reduces the risk of stroke among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin and an LDL-cholesterol level greater than 100 mg/dL (2.6 mmol/L).