Management of Acute Ischemic Stroke

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Stroke is the third leading cause of death and the leading cause of disability in the United States and is associated with a tremendous cost burden to society [1]. Most strokes are ischemic, but about 15% of strokes are caused by intracerebral or subarachnoid hemorrhage. Currently, there is only one drug approved by the US Food and Drug Administration (FDA), intravenous tissue plasminogen activator (tPA), for the treatment of acute ischemic stroke within 3 hours of symptom onset [2]. Many stroke patients do not receive intravenous tPA, however, most commonly because they present beyond the 3-hour therapeutic window. More recently developed therapeutic strategies offer the hope of safe and effective treatment beyond the 3-hour time window in selected patients. This article is an update of a recent publication that reviewed established and novel treatments for acute ischemic stroke and the management issues that may arise in the first hours to days after symptom onset [3]. Blood pressure management, management of intracranial hypertension, and temperature management are discussed in greater detail elsewhere in this issue.

Initial management

The initial management of acute ischemic stroke involves medical stabilization, including airway protection and ventilatory and hemodynamic
support, followed by neurologic assessment, brain imaging, and evaluation of the appropriateness of thrombolytic therapy [4,5].

**Airway and ventilatory support**

Patients with acute stroke are at risk for respiratory failure from aspiration and pneumonia [6,7] often in the setting of difficulty protecting the airway and clearing secretions because of facial or bulbar weakness or an altered level of consciousness [8]. Hypoxemia may worsen the injurious effects of cerebral ischemia, and patients must be monitored closely with a goal to keep oxygen saturation greater than 95% [4]. If a patient requires endotracheal intubation, short-acting sedatives should be used, and the hemodynamic changes associated with intubation should be minimized [5,9,10]. No prospective trials have been undertaken to establish the ideal mode of ventilation in intubated stroke patients. A commonly used mode for patients who are awake but in need of airway protection is pressure support ventilation, whereas synchronized intermittent mandatory ventilation or assist control ventilation is recommended for patients who have intracranial hypertension or are comatose [5]. Excessive positive end-expiratory pressures (ie, > 10 cm H₂O) may be deleterious in patients with elevated intracranial pressure (ICP) [11,12].

Mechanically ventilated patients frequently require sedation; however, sedatives may cause hypotension and additional brain injury by lowering cerebral perfusion pressure [13–15]. Propofol, popular because of its short duration of action, has been associated with a “propofol infusion syndrome” when used at high doses for prolonged periods. This syndrome originally was described in pediatric patients, but it also can occur in adults. It presents with metabolic acidosis, rhabdomyolysis, hypotension, bradyarrhythmias, and death [16]. Frequent discontinuation of sedatives is indicated to monitor carefully for changes in the patient’s neurologic status.

**Blood pressure and fluid management**

Patients with acute ischemic stroke often have elevated blood pressures in the first few days after symptom onset. Elevated blood pressure may occur for a variety of reasons, including physiologic compensation for cerebral ischemia, increased ICP, pain, or long-standing underlying hypertension [4]. Theoretic advantages of treating hypertension in acute ischemic stroke include concerns for hemorrhagic transformation of the ischemic infarct and worsening cerebral edema. Lowering blood pressure may compromise cerebral blood flow in the area surrounding the infarct, however, resulting in stroke extension.

In normotensive individuals, cerebral blood flow is maintained over a wide range of mean arterial pressures (50–150 mm Hg) [17,18]. Chronically hypertensive patients require a higher range of mean arterial pressures to
maintain normal cerebral blood flow [19–21]. Because many stroke patients have long-standing hypertension, blood pressure lowering may result in cerebral hypoperfusion and worsening ischemia. It is generally accepted that elevated blood pressures should not be lowered, unless the patient has received thrombolytic treatment; has a hypertensive emergency (aortic dissection, hypertensive encephalopathy, acute renal failure, acute pulmonary edema, or acute myocardial infarction); or has another contraindication to elevated blood pressure, such as recent surgery. In the absence of controlled clinical trials, the American Stroke Association guidelines recommend that antihypertensive agents should be withheld unless the systolic blood pressure is greater than 220 mm Hg or the diastolic blood pressure is greater than 120 mm Hg [20,22–25]. If patients have received thrombolytic therapy, the guidelines advocate maintaining systolic blood pressure less than or equal to 180 mm Hg and diastolic blood pressure less than or equal to 105 mm Hg [2,22–25]. If blood pressure lowering is indicated, it should be instituted cautiously to avoid hypotension. A variety of intravenous agents may be used to lower blood pressures. α- and β-adrenergic blockers (labetalol), calcium channel blockers (nicardipine), and angiotensin-converting enzyme inhibitors (enalaprilat) are preferred in patients with acute stroke because these agents are less likely to cause cerebral vasodilation and ICP elevation, effects that might be anticipated with sodium nitroprusside or hydralazine [4,5,26–30]. Some patients with acute cerebral ischemia resulting from severe extracranial or intracranial vessel stenosis may benefit from induced hypertension [31]. Typically, mean arterial pressure is increased 20% to 25% from baseline using intravenous isotonic fluids, phenylephrine, dopamine, or norepinephrine, while the patient’s neurologic status and hemodynamic stability are monitored closely. The impact of this therapy on stroke outcome is being evaluated in ongoing clinical trials.

In patients with ischemic brain injury, a key therapeutic goal is to maximize brain perfusion and collateral blood flow to the injured area. It is important to assess the patient’s volume status and correct any dehydration. Because stroke patients may be dehydrated on admission, and many of them cannot tolerate intake of oral fluids, normal saline infusions typically are started immediately. Hypotonic fluids should be avoided because these may contribute to worsening cerebral edema and increased ICP [32].

**Neurologic examination**

Assessing the patient for neurologic deficits may be accomplished in an efficient and reproducible manner by using the National Institutes of Health Stroke Scale (NIHSS) [25,33,34]. This is a series of neurologic tests designed to assess the patient’s level of alertness; comprehension; and motor, sensory, visual, and language function (Table 1) [2].
Table 1
The National Institutes of Health Stroke Scale

<table>
<thead>
<tr>
<th>Tested item</th>
<th>Title</th>
<th>Responses and scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Level of consciousness</td>
<td>0 = Alert</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = Drowsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = Obtunded</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 = Coma/unresponsive</td>
</tr>
<tr>
<td>1b</td>
<td>Orientation questions (two)</td>
<td>0 = Answers both correctly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = Answers one correctly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = Answers neither correctly</td>
</tr>
<tr>
<td>1c</td>
<td>Response to commands (two)</td>
<td>0 = Performs both tasks correctly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = Performs one task correctly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = Performs neither task</td>
</tr>
<tr>
<td>2</td>
<td>Gaze</td>
<td>0 = Normal horizontal movements</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = Partial gaze palsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = Complete gaze palsy</td>
</tr>
<tr>
<td>3</td>
<td>Visual fields</td>
<td>0 = No visual field defect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = Partial hemianopsia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = Complete hemianopsia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 = Bilateral hemianopsia</td>
</tr>
<tr>
<td>4</td>
<td>Facial movement</td>
<td>0 = Normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = Minor facial weakness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = Partial facial weakness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 = Complete unilateral paralysis</td>
</tr>
<tr>
<td>5</td>
<td>Motor function arm</td>
<td>0 = No drift</td>
</tr>
<tr>
<td></td>
<td>a. left</td>
<td>1 = Drift before 10 seconds</td>
</tr>
<tr>
<td></td>
<td>b. right</td>
<td>2 = Falls before 10 seconds</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 = No effort against gravity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 = No movement</td>
</tr>
<tr>
<td>6</td>
<td>Motor function leg</td>
<td>0 = No drift</td>
</tr>
<tr>
<td></td>
<td>a. left</td>
<td>1 = Drift before 5 seconds</td>
</tr>
<tr>
<td></td>
<td>b. right</td>
<td>2 = Falls before 5 seconds</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 = No effort against gravity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 = No movement</td>
</tr>
<tr>
<td>7</td>
<td>Ataxia</td>
<td>0 = Absent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = Ataxia in one limb</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = Ataxia in two limbs</td>
</tr>
<tr>
<td>8</td>
<td>Sensory</td>
<td>0 = Normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = Mild sensory loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = Severe sensory loss</td>
</tr>
<tr>
<td>9</td>
<td>Language</td>
<td>0 = Normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = Mild aphasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = Severe aphasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 = Mute or global aphasia</td>
</tr>
<tr>
<td>10</td>
<td>Articulation</td>
<td>0 = Normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = Mild dysarthria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = Severe dysarthria</td>
</tr>
<tr>
<td>11</td>
<td>Extinction or inattention</td>
<td>0 = Normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 = Mild (loss 1 sensory modality)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 = Severe (loss 2 modalities)</td>
</tr>
</tbody>
</table>

Diagnostic work-up

Brain imaging

CT and MRI can assess rapidly the type of stroke (hemorrhagic versus ischemic) and the condition of the cerebral vasculature. Advances in CT and MRI techniques of cerebral perfusion hold the promise of identifying patients with salvageable brain tissue who could benefit from recanalization therapies beyond the 3-hour time window.

The most widely used and available brain imaging technology is CT. A noncontrast head CT scan quickly excludes an intracranial hemorrhage and sometimes reveals an occluded artery that appears hyperdense because of fresh clot in the vessel lumen (Fig. 1A). The admission CT scan also may show early signs of infarction, including swelling of the brain parenchyma (sulcal effacement); hypoattenuation (hypodensity) of the brain parenchyma; or loss of gray-white matter differentiation (Fig. 1B) [35–37]. Early signs of cerebral infarction in the 3-hour time window slightly increase the risk of hemorrhagic transformation after intravenous tPA, but are not considered a contraindication for tPA treatment [38]. A large area of hypodensity on the admission CT scan obtained within the 3-hour time window is uncommon, however, and warrants verification of the accuracy of the reported time of symptom onset. Because a noncontrast head CT scan may fail to detect subarachnoid hemorrhage in approximately 10% of cases, a lumbar puncture to assess for the presence of subarachnoid blood is mandatory in patients who present with a clinical history of a sudden severe headache and a normal brain CT scan [39].

CT angiography of the head and neck may be used to assess the intracranial and cervical circulation for stenoses and occlusions [40]. CT angiography uses a helical scanner to map out a contrast bolus as it passes through the vessels. It requires adequate peripheral intravenous access for injection of an iodine-based contrast bolus (150–170 mL). Although CT angiography increases the incidence of renal dysfunction, this risk is relatively small; in one series of patients undergoing cerebral CT angiography and CT perfusion, only 4 (0.37%) of 1075 subjects had an increase in creatinine equal to or greater than 0.5 mg/dL [41]. CT angiography may be particularly useful in patients who present just outside of the treatment window for intravenous thrombolysis, and who may be candidates for intra-arterial clot lysis because it can provide valuable information as to the location and extent of the clot. CT angiography also may be useful to assess the head and neck vessels in patients who cannot undergo MRI because of the presence of pacemakers or other metal objects in the body, claustrophobia, or critical illness precluding extended periods in a MRI scanner. Perfusion CT assesses cerebral perfusion of the brain by tracking the first pass of an intravenously administered bolus of contrast material using helical CT scanning [42]. This technique is promising because of its ability to measure absolute cerebral
blood flow to help identify the degree of reversibility of brain injury, but it is limited in that not all vascular territories can be imaged completely. Several studies have found that perfusion CT may be capable of differentiating between regions of brain infarction and ischemic penumbra [43]. A complete CT examination including noncontrast CT, CT angiography, and perfusion CT can be performed in approximately 10 minutes [42].

MRI has better resolution of the brain parenchyma and, in particular, evaluates the brainstem and cerebellum with higher resolution than CT [44]. MRI diffusion-weighted imaging (DWI) detects early cytotoxic edema by measuring the random diffusion of water molecules, which is restricted almost immediately in ischemic brain injury because of failure of the energy-requiring active sodium and water transport mechanism. DWI shows an abnormal signal within minutes of ischemia onset, whereas noncontrast brain CT may take several hours for an infarction to become apparent [45–47]. Not all brain lesions with restricted diffusion are caused by cerebral infarcts. Brain tumors, seizures, brain infections, Creutzfeldt-Jakob disease, and toxic-metabolic disorders sometimes also cause areas of brain injury with restricted diffusion on DWI. Magnetic resonance angiography evaluates the blood vessels of the brain and neck. When it is used without a contrast agent, magnetic resonance angiography creates vessel images by taking advantage of the flow voids caused by moving blood in the magnetic field. One of the drawbacks of magnetic resonance angiography is that it may overestimate the degree of arterial stenosis or give the impression of an arterial occlusion when a complete occlusion may not exist.
Contrast-enhanced magnetic resonance angiography is thought to decrease the likelihood of overestimation of the severity of luminal stenosis [48,49].

MRI perfusion-weighted imaging (PWI) was developed to measure relative blood flow in the brain. A bolus injection of paramagnetic contrast agent is given and tracked on the first pass through the brain parenchyma. A variety of parameters may be measured from this injection and displayed on perfusion maps, including bolus arrival time, mean transit time, and relative cerebral blood volume [42,46,50,51]. Perfusion maps may take 5 to 40 minutes of postprocessing time. The use of PWI and DWI may identify patients who would benefit from recanalization therapy outside the established 3-hour time window for intravenous tPA. An example of a patient in the 3- to 6-hour window with a mismatch between a large perfusion deficit and a small diffusion abnormality and a persistent corresponding vessel occlusion is presented in Fig. 2 [52]. The patient received intravenous tPA 3 to

Fig. 2. MRI of the brain with diffusion-weighted imaging (DWI) on the left, perfusion-weighted imaging (PWI) in the middle, and magnetic resonance angiography on the right. (Top row) MRI obtained approximately 5 hours after acute onset of aphasia and right-sided weakness showing a small area of infarction (white) on DWI, a large area of decreased perfusion of the left middle cerebral artery brain territory (white) at risk for infarction on PWI, and absent flow in the left middle cerebral artery flow on magnetic resonance angiography. (Bottom row) MRI obtained 4.5 hours later (after intravenous tissue plasminogen activator [tPA] administration) shows marked improvement in the PWI and reconstitution of flow in the left middle cerebral artery. There is a marked improvement in neurologic function (National Institutes of Health Stroke Scale [NIHSS] changed from 16 to 5) and no growth of the DWI lesion. (Courtesy of Gregory W. Albers, MD, Palo Alto, CA.)
6 hours after symptom onset, which resulted in vessel recanalization and resolution of the PWI deficit. The patient’s neurologic status improved substantially (NIHSS improved from 16 to 5). If the vessel had remained occluded, the DWI lesion likely would have grown to the size of the corresponding PWI lesion, reducing the chances of clinical improvement.

Emergent laboratory evaluation and other tests

In addition to brain imaging, several laboratory tests must be performed expeditiously to evaluate whether the patient is a candidate for tPA, including a complete blood count, coagulation parameters, and serum glucose (Box 1) [2,4,22,53]. An electrocardiogram is indicated in all patients with acute stroke to detect myocardial ischemia and cardiac arrhythmias, such as atrial fibrillation. Blood urea nitrogen and creatinine levels should be checked, in particular in patients who will be exposed to iodine-based contrast agents. In selected patients, one should consider obtaining (1) arterial blood gas measurements; (2) cardiac biomarkers, including troponin and brain natriuretic peptide; (3) liver function tests and ammonia level (for patients with an unexplained altered level of consciousness); (4) chest radiograph (for patients with respiratory distress or hypoxia); (5) blood cultures (for patients with fever raising a concern for septic emboli); (6) urine toxicology screen (for patients with possible substance abuse); (7) electroencephalogram (for suspected seizures); (8) lumbar puncture (for suspected meningitis or subarachnoid hemorrhage); and (9) CT of the cervical spine if neck trauma has occurred or is suspected [4].

Treatment of acute ischemic stroke

Antiplatelet therapy in acute ischemic stroke

For patients who are not eligible for tPA, aspirin is the only antiplatelet drug that has been evaluated in the acute treatment of stroke. The Chinese Acute Stroke Trial enrolled 21,106 patients to receive aspirin, 160 mg/d, or placebo within 48 hours of stroke onset with continued therapy for 4 weeks [54]. The aspirin-treated group had a small but significant decrease in mortality (3.3% versus 3.9%; \( P = .04 \)) and recurrent ischemic stroke (1.6% versus 2.1%; \( P = .01 \)). The International Stroke Trial enrolled 19,435 patients for randomized treatment with aspirin alone (300 mg/d), subcutaneous heparin alone, aspirin and heparin combined, or neither agent within 48 hours of stroke onset [55]. In the aspirin-only group, there were significantly fewer recurrent strokes within the first 2 weeks (2.8% versus 3.9%) and a trend toward a reduction of death or dependence at 6 months (61.2% versus 63.5%). Based on the results of these trials, most experts agree that patients should be treated within 48 hours of ischemic stroke with aspirin [25,53]. In patients who receive tPA, antiplatelet therapy should start 24 hours after thrombolytic therapy [2,4,22,25,53].
Box 1. Characteristics of patients with ischemic stroke who could be treated with recombinant tissue plasminogen activator

Diagnosis of ischemic stroke causing measurable neurologic deficit
Neurologic signs should not be clearing spontaneously
Neurologic signs should not be minor and isolated
Caution should be exercised in treating a patient with major deficits
Symptoms of stroke should not suggest subarachnoid hemorrhage
Onset of symptoms less than 3 hours before beginning treatment
No head trauma or prior stroke in previous 3 months
No myocardial infarction in the previous 3 months
No gastrointestinal or urinary tract hemorrhage in previous 21 days
No major surgery in the previous 14 days
No arterial puncture at a noncompressible site in the previous 7 days
No history of previous intracranial hemorrhage
Blood pressure not elevated (systolic <185 mm Hg and diastolic <110 mm Hg)
No evidence of active bleeding or acute trauma (fracture) on examination
Not taking an oral anticoagulant, or if anticoagulant being taken, international normalized ratio is 1.7 or less
If receiving heparin in previous 48 hours, activated partial thromboplastin time must be in normal range
Platelet count equal to or greater than 100,000 mm$^3$
Blood glucose concentration equal to or greater than 50 mg/dL ($\geq$2.7 mmol/L)
No seizure with postictal residual neurologic impairments
CT does not show a multilobar infarction (hypodensity greater than one third cerebral hemisphere)
Patient or family members understand the potential risks and benefits from treatment

Intravenous thrombolytic therapy within the 3-hour time window

Intravenous thrombolytic therapy within the 3-hour time window

Intravenous thrombolytic therapy beyond the 3-hour time window

The European Cooperative Acute Stroke Study (ECASS) consisted of two trials evaluating the use of intravenous tPA within 6 hours of symptom onset in patients with a moderate-to-severe hemispheric stroke [60,61]. ECASS I [60] used 85% of the dose for myocardial infarction (1.1 mg/kg,
maximum dose 100 mg), and ECASS II [61] used 75% of the dose for myocardial infarction (0.9 mg/kg, maximum dose 90 mg). In ECASS I, 620 patients were enrolled, but 17% had protocol violations mainly because of misinterpretations of the admission brain CT scans. After excluding the patients with protocol violations, modified Rankin scores (asymptomatic or minimal disability) were significantly better in the tPA group compared with the placebo group. Among all patients enrolled in ECASS I, there was a 20% symptomatic intracranial hemorrhage rate in the treatment group compared with 7% in the placebo group ($P < .001$). This increased rate of hemorrhage in ECASS I likely is related to the tPA dose (1.1 mg/kg, 100 mg maximum), which was substantially higher than in the NINDS tPA study. In ECASS II, 800 patients were enrolled with a primary end point of 3-month favorable outcome defined as a modified Rankin score of 0 to 1 (asymptomatic or no significant disability despite symptoms). The tPA-treated group faiored slightly better at 3 months than the placebo group with a 3.7% higher percentage of patients with favorable outcomes [4,53,60,61].

The Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke trial was a randomized, placebo-controlled trial evaluating the use of 0.9 mg/kg of intravenous tPA in the 3- to 5-hour treatment window [62]. The study was stopped early when interim analysis revealed a low likelihood of benefit in the treatment group. Several clinical trials evaluated intravenous streptokinase for acute stroke in Europe and Australia. The Multi-center Acute Stroke Trial—Italy and Multi-center Acute Stroke Trial—Europe used a 6-hour time window for intravenous treatment with 1.5 million U of streptokinase (100% of myocardial infarction dosage) [63,64]. The Australia Streptokinase Trial used the same dose, but shortened the time window to 4 hours [65]. All three trials were stopped early because of an unacceptable high number of deaths and symptomatic intracranial hemorrhages in the treatment groups.

**Newer thrombolytic and antiplatelet agents**

Recent studies have evaluated alternative thrombolytic agents, such as ancrōd (Viprinex), a viper-derived enzyme that cleaves fibrinogen and promotes endogenous release of plasminogen activator from the vessel wall [4,66–68]. The phase III Ancrod Study compared intravenous Ancrod with placebo within 6 hours of stroke symptom onset and found no difference in 3-month functional success defined as survival with a Barthel index of greater than or equal to 95 (or return to prestroke value) between the treated group (42%) and the placebo group (42%) [69]. Desmoteplase, a protease found in vampire bat saliva, is similar to human plasminogen activator, but in laboratory models works faster and causes a more sustained vessel recanalization compared with tPA. Based on promising phase II trial results (DEDAS and DIAS trials), it was evaluated in the DIAS 2 trial in the
3- to 9-hour time window for acute stroke patients with a presumed penumbra based on MRI or CT imaging results [70,71]. The preliminary results of this trial were presented at the 2007 European Stroke Conference and show no significant difference in 3-month clinical outcome between the desmoteplase-treated and the placebo groups [72].

Glycoprotein IIb/IIIa antagonists also are being evaluated alone (AbESST, SaTIS, SETIS) and in combination with low-dose intravenous tPA (the Clear Stroke Trial) [73–76]. The ReoPro Retavase Reperfusion of Stroke Safety Study—Imaging Evaluation trial is assessing the use of abciximab alone and in conjunction with escalating doses of reteplase. Preliminary results suggest promise for the combination therapy, but not for abciximab alone [77].

Although several novel pharmacologic agents hold promise for acute ischemic stroke patients, current care of patients with acute ischemic stroke still emphasizes NINDS- and FDA-defined use of intravenous tPA dosed at 0.9 mg/kg with a maximum dose of 90 mg. The risk of symptomatic intracranial hemorrhage is approximately 6% when the NINDS- and FDA-approved guidelines are strictly adhered to (see Box 1).

**Intra-arterial thrombolysis**

Direct administration of intra-arterial thrombolytic agents into the clot, while passing the catheter through the clot and mechanically disrupting it, allows for a lower tPA dose and a decreased risk of systemic hemorrhagic complications. A disadvantage of intra-arterial thrombolytic therapy is the time and expertise required for catheterization, restricting this therapeutic modality to medical centers that have interventional neuroradiologists and critical care services available 24 hours a day.

Prolyse in Acute Cerebral Thromboembolism (PROACT) was a randomized clinical trial evaluating the efficacy of intra-arterial prourokinase plus intravenous heparin compared with placebo plus intravenous heparin in patients presenting with middle cerebral artery occlusions less than 6 hours old [78,79]. Mechanical disruption of the clot was not permitted. PROACT I [78] randomized 46 patients and showed that intra-arterial prourokinase infusion was associated with superior recanalization rates compared with placebo. The symptomatic intracranial hemorrhage rate was 15.4% in the prourokinase group versus 7.1% in the placebo group. In PROACT II [79], there was a statistically significant benefit with 40% of prourokinase-treated patients having a good 3-month functional outcome (modified Rankin score ≤2) compared with 25% of the control group. Symptomatic intracranial hemorrhage occurred in 10% of the prourokinase group and 2% of the control group (P = .063). Because prourokinase is not available in the United States for clinical use, tPA and urokinase have been used instead for intra-arterial thrombolysis with favorable outcomes in selected patients [53,78,79].
Intra-arterial thrombolytic therapy for acute stroke is not approved by the FDA, but may be considered in patients with middle cerebral artery occlusions who can be treated within 3 to 6 hours after symptom onset and who have no (or minimal) signs of infarction on their baseline CT scans [4,53]. Given the high mortality associated with basilar artery and internal carotid artery bifurcation (carotid T) occlusions, patients with these lesions also may be considered for intra-arterial thrombolytic therapy on a case-by-case basis [4,53].

Combined intravenous and intra-arterial thrombolysis

The combination of intravenous and intra-arterial thrombolysis has been investigated in several pilot studies and may be more effective than either therapy alone in patients with acute, very large vessel occlusions. The National Institutes of Health Interventional Management of Stroke trial I (IMS I) investigated the feasibility and safety of a combined intravenous and intra-arterial approach to recanalization in patients with ischemic stroke and a substantial neurologic deficit (NIHSS \( \geq 10 \)) [80]. The study enrolled 80 patients, and their outcome was compared with historical intravenous tPA controls. The patients received 0.6 mg/kg of intravenous tPA over 30 minutes within 3 hours from stroke symptom onset followed by intra-arterial tPA within 5 hours if a vessel occlusion was still present on angiography. The 3-month mortality rate and the symptomatic intracerebral hemorrhage rate in IMS patients were similar to intravenous tPA–treated patients in the NINDS tPA Stroke Trial. IMS subjects showed a nonsignificant trend toward better clinical outcomes than historical intravenous tPA controls (odds ratio 1.35; 95% confidence interval, 0.78–2.37). The results of this study and other pilot studies suggest that a combined intravenous plus intra-arterial approach to recanalization is feasible and safe. Further studies assessing the efficacy of this combined approach to recanalization are presently ongoing and have incorporated the use of endovascular mechanical devices.

Mechanical thrombolysis

Several endovascular devices have been developed in recent years to remove clots from the cerebral circulation. These devices have been tested in patients with acute stroke who are ineligible for or who failed intravenous tPA treatment [81–85]. The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) retrieval device has been studied most extensively and was approved by the FDA for use in acute stroke patients who are ineligible or fail intravenous tPA therapy [85]. The device is deployed just beyond the clot with release of two nitinol helices and pulled back into the clot with the remainder of the helices deployed (Fig. 3). It is twisted three to five times to capture the clot better. A balloon is inflated in the internal
carotid artery temporarily to prevent forward flow, while the clot is re-coiled into the positioning catheter and out the body. The MERCI device was tested in an uncontrolled, nonrandomized trial conducted in two parts [85]. The trial enrolled 151 patients who had stroke symptom duration of 3 to 8 hours or less than 3 hours with a contraindication for tPA. Patients also had a substantial neurologic deficit (NIHSS ≥8) and an occlusion of a treatable vessel. Partial or complete recanalization was achieved in 46% of patients on intention-to-treat analysis, and almost half (46%) of these had good neurologic outcomes at 90 days (modified Rankin score of 0–2). Clinically significant procedural complications were reported in 7% of patients. The Multi-MERCI trial tested a newer device (L5) and allowed pretreatment with intravenous tPA [86]. With the newer device this trial, although not statistically significant, seemed promising for better recanalization rates of 68% versus 60% ($P = .15$), lower mortality (35% versus 44%, $P = .12$), and higher favorable outcomes (35% versus 28%, $P = .19$) compared with the MERCI trial [86]. Further studies of the MERCI device are forthcoming in the MR-Rescue and the IMS III trials.

Primary angioplasty and stenting have been shown to be superior to thrombolytic therapy in patients with acute myocardial infarction. This method is most effective in atherosclerotic arteries that have in situ thrombus rather than in blood vessels that are occluded by embolic material [81,87]. Many strokes are caused by artery-to-artery embolism or cardioembolism, however, and these types of clots tend to rebound into an occlusive position despite angioplasty. With further technologic refinements, angioplasty and stenting may play a more important role in the management of acute ischemic stroke in the future [88,89].
Neuroprotective strategies

Many neuroprotective agents that were promising in laboratory models of focal ischemia have not shown benefit in clinical studies, partly because of limitations in trial design. Interest in neuroprotective agents for patients with acute ischemic stroke remains, however, and several phase 3 studies are presently ongoing. One of the most robust neuroprotective strategies in experimental stroke models is mild-to-moderate hypothermia (2°C–5°C below normal brain temperature) [90–92]. Hypothermia consistently has been associated with a marked reduction in ischemic damage and improved behavioral outcomes in these models. The beneficial effects seem to be greatest when hypothermia is initiated early. The therapeutic window of mild hypothermia in patients with acute ischemic stroke is unknown, but likely to be limited to several hours after ischemia onset. The feasibility of hypothermia for acute ischemic stroke patients has been tested in several clinical pilot trials. The Cooling for Acute Ischemic brain Damage study was a phase 2 randomized clinical trial using hypothermia in patients less than 12 hours from stroke onset. There was no significant clinical benefit in 18 patients treated with hypothermia compared with 22 patients who received standard medical therapy. The study showed, however, that endovascular cooling at 33°C was feasible and tolerated by most patients [93]. The Intravascular Cooling for the Treatment of Stroke—Longer window trial is presently ongoing. This is a multicenter, controlled, randomized trial designed to investigate the feasibility and safety of a combination of therapeutic hypothermia with intravenous tPA in the 0- to 6-hour window in awake stroke patients [94].

The Stroke-Acute Ischemic NXY-059 Treatment (SAINT) trials were designed to evaluate the therapeutic benefit of intravenous NXY-059, a nitrone radical trapping agent, administered within 6 hours of stroke onset [95,96]. The SAINT I trial enrolled more than 1700 patients with acute ischemic stroke and showed a modest, but statistically significant ($P = .038$) improved outcome in the treatment group as measured by the modified Rankin scale at 90 days; however, the definitive SAINT II trial, which enrolled more than 3300 patients, did not confirm these results [95,96]. Ongoing phase III trials evaluating neuroprotective agents in acute ischemic stroke include the Field Administration of Stroke Therapy—Magnesium trial assessing the benefit of intravenous magnesium within 2 hours from stroke onset and the Albumin in Acute Stroke study, a trial of high-dose albumin within 5 hours of symptom onset [97–99].

Anticoagulation in acute ischemic stroke

There is no evidence to support urgent anticoagulation to prevent stroke recurrence or extension in patients with acute stroke [25,53,100]. Intravenous heparin infused for 7 days was evaluated in a small randomized, controlled study with 225 patients with acute ischemic stroke [101]. No
significant difference in stroke progression or neurologic outcome was found between the treatment and the control groups. Analysis of the combined heparin groups from International Stroke Trial showed that a decreased recurrent stroke risk at 14 days was offset by an increased risk of intracranial hemorrhage [55]. The low-dose heparin group (5000 U twice a day) had decreased mortality with only a slight and nonsignificant increase in bleeding risk. The low-dose heparin in combination with aspirin had the lowest rate of stroke recurrence and no significant increase in bleeding risk compared with patients on only low-dose heparin. A subgroup analysis of patients who presented with atrial fibrillation and acute ischemic stroke showed a significant reduced risk of recurrent ischemic strokes (4.9% versus 2.8%), but the increased risk of intracranial hemorrhage negated any potential benefits (2.1% versus 0.4%) at 14 days [53,55].

Studies evaluating low-molecular-weight heparins in acute ischemic stroke failed to show a beneficial effect [102–105]. In a subgroup analysis of the TOAST trial, however, better outcomes were observed in patients with stroke caused by large artery atherosclerosis [103,105,106]. In a recent study among Asian stroke patients with large artery occlusive disease (intracranial and extracranial), low-molecular-weight heparin (nadroparin) overall did not support a significant benefit over aspirin in acute stroke patients [107]. Benefits observed in secondary outcome measures, however, may warrant further study of low-molecular-weight heparins in acute stroke patients attributed to large artery atherosclerosis.

Complications of stroke

Hemorrhagic transformation

A feared complication of thrombolytic therapy in stroke patients is intracranial hemorrhage. Symptomatic intracerebral hemorrhage occurs in approximately 6% of patients receiving intravenous tPA for acute ischemic stroke and has been associated with high morbidity and mortality [2,108]. Risk factors for symptomatic intracerebral hemorrhage after thrombolytic therapy include symptom severity, early infarct signs on admission brain CT, older age, elevated systolic blood pressure, low platelet count, elevated serum glucose, history of diabetes, history of congestive heart failure, longer time to treatment, and low levels of plasminogen activator inhibitor [109–120]. The presence of one or more of these risk factors should not be considered a contraindication to tPA treatment, however, in a patient who otherwise qualifies based on the NINDS criteria.

The biologic half-life of tPA at the clot site is approximately 45 minutes, and most tPA-related intracranial hemorrhages occur in the first few hours after treatment. If a patient has a significant neurologic change during intravenous tPA administration, the infusion should be stopped, and an emergent head CT scan should be obtained. Laboratory tests should be
performed immediately, including coagulation parameters, fibrinogen, and complete blood count with platelets. If a symptomatic intracerebral hemorrhage is diagnosed, emergent infusion of fresh frozen plasma (5–10 mL/kg) and cryoprecipitate (0.1 bag/kg) is recommended [121].

Cerebral edema

Patients with ischemic stroke with cerebral edema and mass effect are at risk for brain herniation, brainstem compression, coma, and death. Examples are patients with large hemispheric infarctions involving the middle cerebral artery territory and patients with large cerebellar infarctions. Mass effect caused by ischemic infarcts typically peaks 3 to 5 days after symptom onset. The clinical examination is more sensitive in detecting worsening cerebral edema, local tissue shifts, and impending uncal or transtentorial herniation than continuous ICP monitoring because the clinical deterioration caused by regional tissue injury and compression precedes a global increase in ICP in most patients [5,122,123].

In patients with suspected elevated ICP, initial management should consider adequacy of airway, breathing, and circulatory function. The head should be elevated 30 degrees to decrease ICP and optimize cerebral venous return [124,125]. Hyperosmolar therapy should be instituted using mannitol, hypertonic saline, or both [126–128]. Mannitol extracts intracellular and interstitial water from the brain. This agent also is a free radical scavenger, inhibits programmed cell death, and lowers blood viscosity [129]. It is administered as a 0.5 to 1 g/kg loading dose and can be followed by boluses of 0.25 g/kg every 6 hours. The main complications associated with mannitol use are hypovolemia, hypotension, and electrolyte disturbances resulting from osmotic diuresis. Hypertonic saline has been proposed as an alternative to mannitol and may be of particular advantage in hypovolemic patients. Rebound edema may occur after abrupt cessation of mannitol or hypertonic saline [128]. Experimental and clinical studies suggest potential benefits of hypertonic saline over mannitol in the treatment of stroke-related brain edema and increased ICP [130,131]. More details on the treatment of increased ICP and the use of hyperosmolar therapy can be found elsewhere in this issue. Because of the concern of compromising cerebral blood flow, hyperventilation should be used only in emergency situations and as a temporizing measure until more definitive therapies can be initiated. Corticosteroid therapy, although effective in decreasing cerebral edema in patients with brain tumors and brain abscesses, does not improve cerebral edema associated with ischemic or hemorrhagic stroke and ought to be avoided because corticosteroids are of no benefit and may worsen outcome [132].

Craniectomy has been proposed as a lifesaving measure in patients with large hemispheric infarction accompanied by mass effect space-occupying edema (Fig. 4). The goal of surgery is to reverse mass effect and brain tissue shifts, decrease ICP, improve cerebral perfusion, and prevent secondary
injury. Several observational studies demonstrated a decrease in mortality and improved neurologic outcome, in particular in young patients (age <60 years) with hemispheric infarctions who underwent decompressive hemicraniectomy when compared with historic controls [133–135]. Based on these encouraging reports, three randomized controlled trials were undertaken in Europe to assess the beneficial effect of decompressive surgery in patients with space-occupying hemispheric strokes. A meta-analysis combining data from the three studies was recently published and demonstrated that decompressive hemicraniectomy reduced mortality and improved functional outcome [136]. A substantial proportion of survivors (40%) had a 12-month modified Rankin scale score of 4, however, leading the authors to conclude that “the decision to perform decompressive surgery should be made on an individual basis in every patient” [136]. Decompressive surgery also may benefit patients with large cerebellar infarctions, in particular patients with hydrocephalus, brainstem compression, and neurologic deterioration.

**Deep venous thrombosis**

Deep venous thrombosis and pulmonary embolism are a cause of early death in 5% of stroke patients [137]. Low-dose heparin or low-molecular-weight heparin may be used for prevention of deep venous thrombosis [53]. In the PROTECT study, citraparin, a low-molecular-weight heparin, was found to be at least as effective as unfractionated heparin (5000 units

Fig. 4. Nonenhanced CT scan 3 days after a right middle cerebral artery territory infarction that required a hemicraniectomy to decrease tissue shifts and prevent transtentorial herniation and death.
subcutaneous three times a day) in preventing proximal deep venous thromboembolism, pulmonary embolism, and death related to venous thromboembolism in patients with acute ischemic stroke [138]. Major bleeding events were similar between the citaparin (1.1%) and the unfractionated heparin (1.8%) treated groups [138]. In the PREVAIL study, enoxaparin significantly reduced the risk of thromboembolism (relative risk reduction 43%) compared with unfractionated heparin (5000 units subcutaneous twice a day) \((P = .0001)\) [139]. Symptomatic intracranial hemorrhage and extracranial major hemorrhages were similar between the two groups [139]. Patients who have received thrombolytic therapy should not receive anticoagulation therapy for deep venous thrombosis prophylaxis in the first 24 hours [2,4,22,25,53]. Sequential compression devices are indicated in nonambulatory stroke patients who are unable to receive heparin or low-molecular-weight heparin [53].

**Hyperglycemia**

Hyperglycemia has been associated with larger cerebral infarct volumes in animal models [140]. In humans, worsened outcomes have been reported in patients with elevated admission glucose levels [141]. Hyperglycemia has also been associated with increased cerebral edema volumes and higher hemorrhagic transformation rates with or without intravenous tPA administration [113,142,143]. Stroke patients often have surges in their blood glucose levels because of the sympathetic stress response in the acute phase [4]. Based on these observations it is recommended to avoid dextrose-containing intravenous infusions and serially to check blood glucose and adequately correct elevated blood sugars with short-acting insulin. Further studies are needed to investigate the benefit of tight blood glucose control on stroke outcome [144].

**Fever**

Hyperthermia adversely affects stroke outcome in animal models and in observational clinical studies [91,145–147]. Proposed mechanisms by which hyperthermia may worsen outcome include promotion of an inflammatory response, an increase in release of excitotoxic amino acids, and an increase in cerebral metabolic demand in an already compromised cerebral blood flow state [147–149]. Pneumonia and urinary tract infections are common in stroke patients and must be worked-up aggressively in a febrile patient. Deep venous thrombosis also may cause fevers and should be considered in patients with unexplained fevers. Further studies are needed to evaluate the therapeutic impact of antipyretic agents and cooling therapies in acute stroke. A detailed discussion on temperature management in patients with neurologic injuries can be found elsewhere in this issue.
Summary

Intravenous tPA should be administered to all patients with acute ischemic stroke who present within 3 hours of stroke onset and meet the NINDS inclusion and exclusion criteria. The risk of symptomatic intracranial hemorrhage with intravenous tPA is approximately 6%. Intra-arterial tPA and mechanical thrombectomy are alternative treatment strategies for acute stroke patients who are ineligible for or fail intravenous tPA treatment. Further studies are needed to assess the benefit of these treatments. Patients with acute ischemic stroke should be maintained euglycemic, euvoletic, and normothermic. Permissive hypertension may be beneficial, but in patients receiving tPA blood pressures should be maintained at or less than 180/105 mm Hg. Patients with life-threatening cerebral edema from hemispheric infarctions require hyperosmolar therapy and may benefit from early surgical decompression. Novel management strategies under investigation include the use of multimodal imaging to identify patients who might benefit from tPA beyond the 3-hour time window, new thrombolytic agents, and neuroprotective therapies.

References


