The golden hour

Performing an acute ischemic stroke workup

Abstract: Ischemic stroke is a medical emergency resulting from an embolic or thrombotic occlusion of an intracranial artery. The purpose of this article is to provide acute care nurse practitioners a summary of recent updates on the rapid evaluation and workup for patient selection and treatment with I.V. fibrinolysis.

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Stroke has declined from the third to the fourth leading cause of death in the United States.[1] This is the result of decades of interventions focused on hypertension control and aggressive public health campaigns emphasizing early recognition of stroke symptoms with rapid evaluation and treatment through established stroke systems of care.[2] Despite the excellent progress in reducing stroke-related deaths, the burden of disability from stroke remains consistent. Stroke continues to be the leading cause of disability in the United States, contributing to poor quality of life and billions of dollars in healthcare cost.[3]

Ischemic stroke, resulting from embolic or thrombotic occlusion of an intracranial artery, accounts for 87% of all strokes.[3] The administration of I.V. fibrinolysis with recombinant tissue plasminogen activator (rt-PA) within 3 to 4.5 hours of stroke symptoms' onset is the only current treatment shown to reduce disability from ischemia stroke.[4,5] Reduction in disability following stroke will therefore require continued efforts to improve patients' access to hospitals capable of providing rapid evaluation and treatment with rt-PA, coupled with proper patient selection to avoid serious complications (most commonly hemorrhage).

New guidelines for the early management of acute ischemic stroke include the importance of establishing regional stroke systems of care (SSOC) that incorporate emergency medical transport to designated stroke centers and the use of telemedicine consultation and aeromedical transport to increase patient access and limit delays in stroke treatment.[6] Nurse practitioners (NPs) are increasingly being used in roles that interface with the SSOC for acute ischemic stroke, including emergency identification, evaluation, transport, and hospital management. The purpose of this article is to provide acute care NPs a summary of recent updates on the rapid evaluation and diagnostic workup required for patient selection and treatment of acute ischemic stroke with I.V. fibrinolysis.

Prehospital care

Emergency medical services within an SSOC provide the full scope of prehospital stroke care, including 911 activation and dispatch, emergency medical response, triage and stabilization in the field, and ground or air ambulance transport.[7] Evidence supports the importance of limiting delays in treatment. One proposed approach to reduce delays is through preferential triage and transport of patients with suspected stroke to hospitals certified as primary or comprehensive stroke centers. Certified hospitals are endorsed by the American Heart Association and the American Stroke Association (AHA/ASA) and Brain Attack Coalition because these facilities have well-established protocols and processes for providing rapid evaluation and treatment for acute ischemic stroke and improved outcomes for treating eligible stroke patients with rt-PA.[8,9] Current preferential triage policies will generally apply only to urban areas, as there are relatively few primary stroke centers or comprehensive stroke centers available in rural areas.

The inclusion of acute stroke ready hospitals (ASRH) as a useful alternative for preferential triage in rural areas is a relatively new concept. ASRHs should have well-developed collaboration within a regional SSOC and established relationships with certified primary or comprehensive stroke

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centers for additional support and to minimize delays. This collaboration could include the use of telemedicine, teleradiology, and intrafacility transport once patients are diagnosed and initial treatments are delivered. It is hoped that ASRHs have the potential to greatly extend the reach of SSOC into underserved regions.[6]

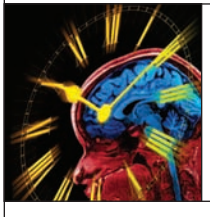
Emergency triage: The initial assessment

A patient presenting with symptoms of stroke meets triage criteria for Emergency Severity Index level 2.[10] Such patients should receive the same triage priority as any patient presenting with an unstable condition. The goals of triage and the initial assessment are to first ensure medical stability in terms of airway, breathing, and circulation. Then, an initial, brief, focused assessment is completed to confirm that presenting symptoms are consistent with stroke and to determine if the onset of stroke symptoms is within the time window for treatment with I.V. rt-PA.

Successful triage must include dependable methods for recognizing stroke symptoms. Standardized scales can expedite completion of the major components of a neurologic exam but do not make the diagnosis of stroke. The National Institutes of Health Stroke Scale (NIHSS) is often used to confirm the presence of stroke symptoms and to quantify the degree of neurologic deficits.[11] Sudden-onset focal neurologic impairment distinguishes stroke from other neurologic conditions. Cardinal symptoms predictive of stroke are sudden motor and sensory deficits, including facial droop, hemiparesis, isolated weakness of the arm or leg, and slurred speech.[12] Less recognized symptoms include sudden-onset dizziness (specifically vertigo), loss of coordination or balance, gait disturbances, and vision loss in one or both eyes. Patients with acute stroke might also present with apparent confusion resulting from expressive or receptive aphasia, visuospatial neglect, or an early sign of a major thrombosis in the basilar artery, affecting the memory centers of the brain (hippocampus). Acute-onset quadriparesis, loss of consciousness, and respiratory failure are stroke symptoms that result from thrombosis of the basilar artery.[13]

Determining the time of stroke symptoms onset is crucial and drives subsequent clinical decisions related to the patient's eligibility for I.V. fibrinolysis. The time of the symptoms' onset is defined as the time at which the patient was last known to be at his or her prior baseline without the signs and symptoms of the current stroke.[14] Ascertaining when the patient was "last seen normal" must be done quickly and will require corroboration of events with family members and other eye witnesses, as the patient is often unable to provide a reliable history. The "last seen normal" time in patients who present with wake-up stroke symptoms is usually when the patient went to bed, unless there was some awakening during which it is certain that the patient was normal.

Acute ischemic stroke patients who present with a symptom onset of 3 hours or less are within the FDA-approved time window for I.V. rt-PA administration. This time window was established based on the initial National Institute of Neurological Disorders and Stroke (NINDS) trials and is consistent with the U.S. FDA labeling for rt-PA administration.[15] The European Cooperative Acute Stroke Study III showed a favorable risk-benefit ratio for acute ischemic stroke patients who received I.V. rt-PA within 3 to 4.5 hours of stroke symptoms' onset.[5] The AHA/ASA endorsed the extended time window of 3 to 4.5 hours for I.V. administration of rt-PA in 2009, but the FDA did not; this was possibly related to an earlier, smaller study that showed worse outcomes with a 5-hour time window.[16,17] Additionally, a quasi-randomized stroke trial conducted in the United Kingdom suggested modest benefits from I.V. rt-PA administered within a 6-hour time window. However, the FDA still has not approved the extended time window.[18]



The sooner I.V. rt-PA is administered after the onset of stroke symptoms, the better the outcome.

The golden hour evaluation and workup

Benefits for I.V. rt-PA in acute ischemic stroke are time-dependent. The sooner I.V. rt-PA is administered after the onset of stroke symptoms, the better the outcome, especially for patients with moderately severe stroke.[19] A door-to-treatment time of 60 minutes or less is the goal. This 60-minute period is often referred to as the "golden hour" of acute ischemic stroke treatment during which a focused diagnostic workup must be completed to rule out conditions that may mimic stroke as well as contraindications to rt-PA administration.[20]

Implementation of an acute ischemic stroke protocol and an acute stroke team to complete brain imaging and other tests within the golden hour is recommended. Members of a stroke team will vary depending on the needs of the individual hospital. Minimally, the stroke team should consist of providers who complete the initial evaluation, nurses, consulting and admitting physicians, computed tomography (CT) scan technicians, and radiologists. Additionally, lab personnel should be aware of studies that need to be

processed immediately.[21] To optimize the acute ischemic stroke workup, the NINDS has established time targets for critical actions during the golden hour.[22] (See *NINDS time targets for the golden hour workup for acute ischemic stroke.)*

Acute ischemic stroke patients age 18 or older who present within the time window for fibrinolytic therapy meet criteria for I.V. rt-PA. However, there are multiple contraindications for I.V. rt-PA (see *Contraindications for the treatment of acute ischemic stroke with rt-PA).* A rapid evaluation and workup within the golden hour is vital to identify contraindication. The use of an rt-PA checklist can help focus the history and physical exam to facilitate identification of contraindications. It is also important to identify conditions that mimic stroke, although it is inevitable that some conditions that mimic acute ischemic stroke will be treated due to the need for rapid administration of rt-PA. Attempting to completely exclude the relatively rare stroke mimic would unacceptably compromise door-to-needle time for rt-PA administration in the majority of patients that present with actual acute ischemic stroke. Fortunately, for most conditions that mimic acute ischemic stroke, rt-PA treatment is relatively safe but is of no benefit.[23] Conditions that mimic acute ischemic stroke include: seizure, syncope, central nervous system tumor, migraine, hypoglycemia, head trauma, multiple sclerosis, spinal cord injury, systemic infection, viral encephalitis, and alcohol and substance abuse.[6]

Patient and family members should be asked about history of epilepsy, use of insulin or other oral diabetes agents, alcohol and substance abuse, recent falls, known heart conditions, or recent infections. The patient and family should also be asked about conditions that would preclude treatment with fibrinolytic therapy. These conditions include: stroke or head trauma in the previous 3 months, history of intracranial hemorrhage, intracranial neoplasm, arteriovenous malformation or aneurysm, recent intracranial or intraspinal surgery, arterial puncture at a noncompressible site within the last 7 days, active internal bleeding, elevated systolic BP greater than 185 mm Hg, or diastolic BP greater than 110 mm Hg.[6]

The history and the head-to-toe physical exam are focused on identifying conditions that mimic stroke and rt-PA contraindications. The head and extremities should be inspected and palpated for signs of trauma. A tongue laceration may suggest a seizure. Auscultation of the heart is important to identify an irregular rhythm and abnormal rate as well as murmurs. The carotid arteries should be auscultated for bruits and the lungs for adventitious breath sounds and fluid overload. The skin should be inspected for bruises, which may indicate trauma or that the patient is on anticoagulant therapy. Skin, abdomen, and extremities should also be inspected for evidence of surgery or other invasive procedures. A focused neurologic exam should be completed to confirm information obtained from the history and to quantify the severity of stroke symptoms. If the NIHSS has not already been completed, this can be done as part of the physical exam. An accurate body weight should also be obtained early in the evaluation process to prevent dosage errors in preparation for treatment with I.V. rt-PA.[24]

NINDS time targets for the golden hour workup for acute ischemic stroke[6,22]

Clinical action	NINDS time target
Door-to-physician/provider evaluation	10 minutes or less
Door-to-stroke team notification	15 minutes or less
Door-to-completion of CT scan	25 minutes or less
Door-to-interpretation of CT scan	45 minutes or less
Door-to-completion of lab values	45 minutes or less
Door-to-treatment with fibrinolytic therapy	60 minutes or less

Immediate diagnostic tests

In addition to a focused history and physical exam, emergent brain imaging with either noncontrast CT or magnetic resonance imaging (MRI), a serum glucose and oxygen saturation are the essential, immediate diagnostic tests that must be obtained before administration of fibrinolytic therapy.[6] Brain imaging studies are completed to exclude intracranial hemorrhage or nonstroke lesions responsible for neurologic deficits, to identify the degree of ischemic brain injury, and the vascular lesion responsible for the ischemic attack.[25] Blood glucose must be obtained to exclude hypoglycemia and hyperglycemia. Point-of-care blood glucose values can be obtained quickly by finger stick and glucometer. The presence of hypoglycemia can cause neuronal injury and focal deficits that mimic stroke, whereas hyperglycemia augments brain injury in acute ischemic stroke and is associated with deleterious effects.[26,27] Oxygen saturation via pulse oximetry is necessary to exclude ischemic stroke associated with hypoxemia.

Other immediate, recommended tests include an ECG to look for an acute myocardial infarction (MI) and other potential complications, complete blood cell count including platelets, cardiac enzymes and troponin, serum electrolytes, blood urea nitrogen, creatinine, prothrombin time (PT)/international normalized ratio (INR), and activated partial thromboplastin time (aPTT). Treatment with I.V. rt-PA should not be delayed while waiting on results for these studies; however, exceptions include INR and PTT if the patient was recently treated with warfarin or heparin. Among lab values, only blood glucose measurement must precede I.V. rt-PA administration unless

the patient is on anticoagulation or has known bleeding diathesis.[6] It is important to note that with the broader use of newer anticoagulants, such as a direct thrombin inhibitor or factor Xa inhibitor, for stroke prevention in atrial fibrillation, the usual blood tests for anticoagulation do not apply, and at least for the moment, it is not generally recommended to use rt-PA in these patients.[8] However, the use of I.V. rt-PA is reasonable in eligible patients who have not received these medications for at least 2 days.[6]

Other specific tests are also recommended in certain situations. Patients presenting with suspicion of alcohol intoxication or substance abuse should receive a blood alcohol and toxicology screen as well as a liver function tests (for example, alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase [ALP]). An arterial blood gas is needed in the presence of hypoxemia, and chest radiography is necessary if there is suspected lung disease or injury. An electroencephalogram should be obtained if ongoing seizures are suspected, and a pregnancy test is warranted in women of childbearing age.[6] Finally, a lumbar puncture should be completed if there is a suspicion that subarachnoid hemorrhage is the cause of stroke symptoms and brain imaging is negative. Fibrinolytic therapy should not be administered if there is suspicion for subarachnoid hemorrhage because of risk of spinal hemorrhage and subsequent paralysis.[28]

Contraindications for the treatment of acute ischemic stroke with rt-PA[6]

Contraindications based on history

- Stroke or head trauma in the last 3 months
- Previous intracranial hemorrhage
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Recent intracranial or intraspinal surgery
- Arterial puncture at a noncompressible site within last 7 days

Contraindications based on physical exam and clinical findings

- Symptoms suggestive of subarachnoid hemorrhage
- BP consistently elevated (systolic > 185 mm Hg or diastolic > 110 mm Hg)
- Blood glucose < 50 mg/dL
- Active internal bleeding
- Active bleeding diathesis

Contraindications based on hematologic factors

- Platelet count < 100,000/mm^3
- Current anticoagulant use with an INR > 1.7 or PT > 15 seconds
- Heparin use within 48 hours and an abnormally elevated aPTT
- Current use of a direct thrombin inhibitor or direct factor Xa inhibitor

Contraindications based on CT scan findings

- Evidence of hemorrhage
- Evidence of multilobar infarction with hypodensity involving > 33% of the cerebral hemisphere

Relative contraindications

- Minor or isolated neurologic signs
- Spontaneously clearing stroke symptoms
- Major surgery or serious trauma in the last 14 days
- Gastrointestinal or urinary tract bleeding in the last 21 days
- MI in the previous 3 months
- Seizure at the onset of stroke with postictal neurologic impairments
- Pregnancy

Contraindications criteria for treatment within the 3- to 4.5-hour time window

- Age > 80
- Oral anticoagulant use regardless of INR
- Severe stroke (NIHSS score > 25)
- Combination of both previous ischemic stroke and diabetes mellitus

Neuroimaging

Noncontrast CT of the brain is routinely used for emergent brain imaging in acute ischemic stroke because of availability, rapid acquisition, and ease of interpretation. The noncontrast CT is sufficient in identifying hemorrhage as well as other large hypodensities indicating subacute stroke and is cost-effective when compared with other brain imaging modalities.[29] An MRI of the brain can reliably detect hyperacute hemorrhage and has an advantage over CT in detecting very early ischemia with diffusion-weighted imaging techniques; however, it can take longer to complete and interpret.[30] Both acute ischemic stroke and acute hemorrhagic stroke can be reliably diagnosed within the golden hour timeline in centers where MRI is readily available and there are established ultrafast imaging protocols for rapid acquisition and interpretation.[31] Widespread implementation of ultrafast MRI imaging protocols has not been well established, and there are no randomized trials to confirm that MRI is superior to noncontrast CT for selecting patients for I.V. rt-PA.[32,33] Moreover, MRI should only be used during the golden hour for acute ischemic stroke if no delays in treatment are incurred and noncontrast CT remains the only option when patients have contraindications for MRI (for example, implanted devices such as pacemakers).[6]

Early signs of infarction can be identified on noncontrast CT even as early as 3 hours from symptom onset.[29] An in-depth discussion on the types of early infarct signs seen on noncontrast CT is beyond the scope of this

article, but it is important to note that the occurrence, clarity, and degree of early ischemia seen on noncontrast CT are correlated with a higher risk of hemorrhage after I.V. fibrinolysis.[15] Patients with early signs of infarction involving more than one third of the middle cerebral artery (MCA) territory were excluded in pivotal trials that investigated the benefit of rt-PA in the 3- to 4.5-hour window as well as trials investigating intra-arterial fibrinolytic therapy up to 6 hours after symptoms' onset.[34,35] It is not known what treatments would be safe and effective in such patients, although many centers would consider endovascular approaches; however, they have not been shown to be effective in these patients. The new guidelines recommend that treatment with I.V. rt-PA should be avoided in the presence of "frank hypodensity" on noncontrast CT involving more than one third of the MCA territory.[6]

When symptoms of stroke spontaneously resolve to baseline, which occurs with transient ischemic attack or rapidly improved symptoms, rt-PA has often not been given based on exclusion criteria in the NINDS rt-PA trial.[15] However, it has more recently been shown that these patients continue to be at risk for stroke progression or recurrence, particularly in the first 72 hours and in the presence of a large, symptomatic artery plaque.[36] It is not known if rt-PA or some other approach, such as aspirin alone, intravenous heparin, or loading with dual antiplatelet therapy, is best for stabilizing these patients. A rapid referral for carotid endarterectomy or stenting is currently the best approach when the etiology of resolving stroke symptoms is carotid plaque. Several of these different approaches are either currently undergoing study or have been studied, with the best approach still unresolved. Should the symptomatic plaque be in the intracranial circulation, such as the basilar artery or MCA, recent studies do not support endovascular intervention, and current recommendations are for aggressive risk factor management with antiplatelet, antihypertensive, and lipid-lowering therapy.[37] Unfortunately, in the case of intracranial stenosis, the stroke recurrence rate remains high at approximately 15% per year.

BP management

Continuous monitoring of BP is essential during the hyperacute phase of acute ischemic stroke, as poor outcomes are associated with both high and low extremes in BP.[6] Hypertension is common in patients with acute ischemic stroke and is attributable to multiple factors, such as chronic hypertension, sympathetic response, and dysfunction in cerebrovascular autoregulation.[38] Cerebrovascular autoregulation is the brain's response to changes in cerebral perfusion pressure (CPP), and under normal circumstances, CPP automatically adjusts to changes in cerebrovascular resistance via reflex vasoconstriction or vasodilation of the cerebral arterioles. Normally, the cerebral blood flow (CBF) remains relatively constant at about 50 mL per 100 g tissue per minute across a wide range of mean arterial pressure (MAP).[39] Changes in autoregulation are a compensatory response to maintain and even increase CPP and CBF in the presence of brain ischemia. However, evidence suggests that autoregulation becomes dysfunctional with ischemic stroke, and thus, CBF increases or decreases proportionally in response to MAP in the absence of autoregulation. This results in increased brain ischemia in the presence of a low MAP and edema and/or hemorrhage with excessive rise in MAP.[40]

Hypertension should be cautiously approached in patients with acute ischemic stroke with the understanding that rapidly lowering systemic BP can lead to worsening ischemia and deleterious outcomes. It is a delicate balance to maintain CBF at a level that will not worsen ischemia or potentiate intracranial hemorrhage. The current recommendation is to not lower the BP during the initial 24 hours of acute ischemic stroke unless BP is greater than 220/120 mm Hg.[6] The management of hypertension during the golden hour in patients eligible for rt-PA warrants special consideration because the risk of intracranial hemorrhage is compounded in the setting of hypertension and fibrinolytic therapy. Lowering BP in patients eligible for rt-PA is necessary when systolic and diastolic pressures rise above 185 mm Hg or 110 mm Hg, respectively.[6] There is no clear evidence on the best pharmacologic agent for lowering BP during the hyperacute period of acute ischemic stroke. I.V. antihypertensive agents that can be titrated to a MAP goal are best to prevent rapid reduction in BP and CBF. The approach is to lower systolic and diastolic values for safe administration of fibrinolytic therapy when treating hypertension in an rt-PA-eligible patient. There is evidence that the risk of intracranial hemorrhage may be associated with persistent or labile hypertension in patients with acute ischemic stroke, and the decision to abstain from fibrinolytic therapy is reasonable when BP is resistant to treatment.[41] Moreover, BP should be stabilized and maintained at or below 180/105 mm Hg for at least 24 hours post fibrinolytic treatment[6]; therefore, labile and treatment-resistant BP is a red flag when considering fibrinolytic therapy.

Administration of I.V. fibrinolytic therapy

A signed, informed consent is not required before administering fibrinolytic therapy within 3 hours of stroke symptom onset, as rt-PA is the only FDA-approved treatment for acute ischemic stroke in patients meeting eligibility criteria.

However, information about risks and benefits should be provided to the patient and family when a patient is first determined to be eligible for rt-PA. Time should be given to address questions and concerns, and as it is with any treatment decision, the patient has a right to refuse. It is good practice to document (in the patient's medical record) that information was provided, that risks and benefits were discussed, and that the patient and family understand both and agree (or disagree) with the treatment plan.

The dose for I.V. rt-PA is calculated based on the patient's weight, and an accurate weight must be obtained to reduce dosing errors.[24] The dose for alteplase is 0.9 mg/kg up to a maximum dose of 90 mg for treating acute ischemic stroke. Administration is initiated with 10% of the total dose given as an I.V. bolus over 1 minute followed immediately by I.V. infusion of the remainder of the dose over 1 hour.[42] Concurrent monitoring of BP and neurologic status during the infusion is essential. Infusion should be promptly discontinued if there are any changes in neurologic status, and a noncontrast CT scan should be immediately obtained to rule out intracranial hemorrhage.[6]

Patients should be admitted to an ICU, since continued hemodynamic and neurologic monitoring is needed for 24 hours post infusion. Standard post rt-PA BP monitoring is every 15 minutes for 2 hours, every 30 minutes for 6 hours, and hourly for the remainder of the 24 hours after treatment with rt-PA.[6] Antiplatelet or anticoagulation therapy and invasive procedures should be withheld during the subsequent 24 hours. An immediate neurosurgical consultation should be initiated in the event of a post-rt-PA hemorrhage.

A coordinated approach

Appropriate evaluation and treatment with I.V. fibrinolytic therapy can make a critical difference between independence and disability for a patient with acute ischemic stroke. Rapid evaluation and treatment within the golden hour of acute ischemic stroke requires a coordinated, multidisciplinary approach and knowledge of the best practices, therapies, and available management techniques. This article provides NPs in acute care an update on the recent guidelines for evaluation and treatment of a patient presenting within the time window for I.V. fibrinolytic therapy. Knowledge gained will equip NPs to impact stroke care through focused efforts to improve timely evaluation and treatment of patients presenting with acute ischemic stroke. NP

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