**Introduction**

Stroke is the leading cause of serious long-term disability and the fifth leading cause of death in the United States. Each year, over 795,000 people experience a new or recurrent stroke. Of these, approximately 87% are ischemic strokes. Major advancements have been made in the treatment of acute ischemic stroke in the past decade, including the expansion of the IV tissue plasminogen activator (tPA) treatment window from 3 hours to 4.5 hours and the strong recommendation for mechanical thrombectomy in large vessel occlusion strokes. Clinical pharmacists play a critical role in the hyperacute management of ischemic stroke, from assessing candidacy for IV thrombolysis and blood pressure control to preparing and administering urgent pharmacologic therapies. 

**Clinical Presentation**

Acute ischemic stroke should be suspected in any patient presenting with new onset neurological deficits. Rapid assessment, diagnosis, and treatment are essential to minimize permanent injury to brain tissue. Key aspects of the clinical presentation include:

* Signs and Symptoms:
  + Weakness or numbness on one side of the body
  + Facial droop
  + Slurred speech
  + Vision changes
  + Vertigo
  + Loss of coordination
  + Severe headache
* Risk Factors:
  + Older age
  + Hypertension
  + Diabetes
  + Dyslipidemia
  + Atrial fibrillation
  + Prior stroke or TIA
  + Cigarette smoking
  + Obesity
  + Sedentary lifestyle
  + Family history of stroke
* Demographics:
  + Stroke can occur at any age, but risk increases with age
  + Men have a higher incidence than women at younger ages
  + African Americans have higher stroke mortality than Caucasians
  + Geographic region impacts risk, with higher rates in southeastern U.S.

The clinical presentation of acute ischemic stroke can vary considerably depending on the location and extent of infarction. However, recognizing the most common symptoms and risk factors is key for pharmacists to facilitate prompt diagnosis and treatment.

**Pathophysiology**

Acute ischemic stroke occurs when a thrombus or embolism abruptly blocks an intracranial artery, resulting in dramatically reduced blood flow to the brain tissue supplied by that artery. This initiates a complex biochemical cascade involving energy failure, glutamate excitotoxicity, intracellular calcium overload, lipid degradation, and generation of free radicals, ultimately leading to cellular injury and death. The core infarcted area is surrounded by a region of hypoperfused tissue that is functionally impaired but potentially salvageable if perfusion can be restored rapidly. This ischemic penumbra represents the target for acute stroke therapies. The size of the penumbra decreases over time as the metabolic disturbances perpetuate irreversible neuronal injury. Therefore, timely restoration of blood flow is essential to prevent progression of the core infarct and salvage the penumbra.

**Diagnostic Approach to Acute Ischemic Stroke**

Accurate and timely diagnosis of acute ischemic stroke is paramount to delivering appropriate treatment and improving patient outcomes. This diagnostic approach is a comprehensive, step-by-step guide designed for emergency medicine and critical care professionals.

**1. Initial Assessment: The NIHSS Scale**

* Definition: The National Institutes of Health Stroke Scale (NIHSS) is an objective, reproducible scale used to evaluate the severity of neurologic deficits in stroke patients.
* Components: Comprising 11 distinct items, it assesses consciousness, gaze, visual field, facial palsy, arm and leg motor function, limb ataxia, sensory loss, language, speech articulation, and inattention.
* Scoring: The NIHSS score ranges from 0 (indicating no deficit) to 42 (denoting a severe stroke). Stroke severity is categorized as:
  + Mild: NIHSS 1-4
  + Moderate: NIHSS 5-15
  + Moderate/Severe: NIHSS 15-20
  + Severe: NIHSS >20

**2. Medical History and Physical Exam**

* Onset: The exact time of symptom onset or the last known well time is crucial for treatment decisions.
* Symptoms: Focus on abrupt onset of neurological deficits, such as hemiparesis, dysarthria, or visual changes.
* Predisposing Factors: Ask about previous strokes, transient ischemic attacks (TIAs), atrial fibrillation, hypertension, diabetes, and other vascular risk factors.

**3. Brain Imaging**

Differentiating between ischemic and hemorrhagic stroke is essential as their management vastly differs.

* **Non-contrast CT (NCCT):**
  + Use: The primary, rapid modality to exclude hemorrhage, especially prior to thrombolytic therapy.
  + Findings: Early signs include loss of the insular ribbon, sulcal effacement, or the "dense MCA" sign.

* **MRI with Diffusion-Weighted Imaging (DWI):**
  + Use: is very sensitive in detecting acute ischemic changes. While it offers superior resolution and can detect ischemia earlier than CT, its availability in an emergency setting might be limited.
  + Findings:  Acute ischemic regions appear hyperintense on DWI and hypointense on the corresponding apparent diffusion coefficient (ADC) map.

* **CT Angiography (CTA) and MR Angiography (MRA):**
  + Use: These modalities are valuable for visualizing the cerebral vasculature. They can identify the location of vascular occlusions, assess collateral circulation, and inspect for vascular anomalies or dissections.
  + Findings: The site of arterial occlusion, such as the "clot sign" in CTA, can be visualized. MRA provides detailed vascular anatomy without the need for contrast, but CTA is often faster and more readily available in acute settings.

* **CT Perfusion (CTP):**
  + Use: CTP provides dynamic information about cerebral blood flow, volume, and mean transit time. It's instrumental in determining the extent of salvageable penumbra tissue (tissue that's at risk but not yet infarcted) and differentiating it from the irreversibly damaged ischemic core.
  + Findings: Regions with reduced cerebral blood flow but preserved or increased cerebral blood volume suggest penumbra, while areas with both reduced flow and volume indicate infarcted tissue.

**4. Electrocardiogram (ECG)**

* Purpose: To identify potential cardiac sources of emboli, especially atrial fibrillation, and other arrhythmias which could have precipitated the stroke.

**5. Laboratory Investigations**

* Electrolytes: To identify potential metabolic causes or derangements.
* Blood Urea Nitrogen (BUN) and Creatinine: To assess renal function, especially before administering contrast agents or specific medications.
* Glucose: Hyperglycemia or hypoglycemia can mimic stroke symptoms.
* Complete Blood Count (CBC): To evaluate for infection, anemia, or thrombocytosis.
* Prothrombin Time/INR: Essential if considering anticoagulation therapy.
* Troponin: To rule out concurrent myocardial infarction or detect subtle cardiac injuries.

**The diagnostic workup differs based on stroke subtype:**

* For suspected large-artery atherosclerosis, imaging of the extracranial and intracranial vasculature with CTA, MRA, or catheter angiography is important to evaluate for stenosis amendable to revascularization procedures.
* Cardioembolic strokes warrant echocardiography and cardiac monitoring to identify the embolic source and guide anticoagulation.
* Small-vessel disease is a clinical diagnosis based on lacunar syndrome presentation and small, subcortical infarcts on imaging.

### ****Management – Overview****

The key principles in management of acute ischemic stroke are:

* Rapid triage, diagnosis, and determination of stroke subtype - CT or MRI to differentiate ischemic vs. hemorrhagic stroke
* Restore blood flow to ischemic penumbra urgently via IV thrombolysis with fibrinolytics and/or mechanical thrombectomy with stent retrievers
* Supportive care - stabilize airway, breathing, circulation; control blood pressure
* Prevent complications of stroke immobility such as aspiration pneumonia, DVT, skin breakdown
* Initiate secondary prevention strategies like antiplatelets, anticoagulants in AF, statins
* Coordinate care - multidisciplinary team including pharmacy, medicine, neurology, radiology, nursing, rehab services
  + Recombinant tissue plasminogen activator (rt-PA) that binds to fibrin in the thrombus and converts plasminogen to plasmin, resulting in clot breakdown

The timeframe for acute management ranges from the hyperacute period (within 24 hours) focusing on reperfusion and medical stabilization to the acute period (first week) when complications like edema or hemorrhage conversion may occur, to the post-acute period (after one week) when rehab and secondary prevention are paramount.

The specific management approach depends on multiple factors including infarct size, location, patient comorbidities, and institutional resources. However, timely restoration of blood flow via thrombolysis and/or thrombectomy remains the cornerstone of therapy.

### ****Pharmacotherapy****

#### IV Thrombolysis

Alteplase

* FDA approved for treatment of acute ischemic stroke within 3 hours (Class I, Level A) and 3-4.5 hours (Class I, Level B) of symptom onset
* Dose: 0.9 mg/kg (maximum 90 mg), with 10% given as an IV bolus over 1 minute and 90% infused over 60 minutes
* Onset of action within minutes with half-life of 4-5 minutes
* Adverse effects: Hemorrhage, angioedema
* Contraindications:
  + History of intracranial hemorrhage
  + Active internal bleeding
  + Recent intracranial or intraspinal surgery
  + Severe uncontrolled hypertension
  + Intracranial conditions increasing bleeding risk
  + Coagulopathy or platelet count <100,000/mm3
  + Current use of direct thrombin or anti-Xa inhibitors
  + Major surgery or trauma within 3 months
  + Gastrointestinal bleeding within 21 days
  + Age <18 years
  + Warnings: Recent ischemic stroke, major surgery/trauma, bleeding risks

Tenecteplase

* Recombinant tissue plasminogen activator with greater fibrin specificity, longer half-life, faster clearance than alteplase
* Not FDA approved for acute ischemic stroke but may be considered as an alternative to alteplase
* Dose: 0.25 mg/kg single IV bolus (maximum 25 mg)
  + 0.25 mg/kg has lower bleeding rate and equally effective to 0.4 mg/kg
  + Potential advantages over alteplase: More fibrin-specific, easier administration, lower cost
  + Disadvantages: data on efficacy/safety not as robust as alteplase, not widely available, risk of dosing confusion with alteplase

#### Endovascular thrombectomy:

* First-line therapy along with IV tPA for proximal large artery occlusion (ICA, M1 MCA)
* Extends treatment window to 24 hours from symptom onset
* Stent retrievers are preferred (Trevo, Solitaire devices)
* Does not preclude full-dose IV tPA
* General anesthesia avoided to allow neuro checks
* Hemorrhage, vessel injury are procedural risks

#### **Blood Pressure Management**

* For alteplase-treated patients:
  + Goal SBP <185 mm Hg and DBP <110 mm Hg prior to alteplase
  + Goal SBP <180 mm Hg and DBP <105 mm Hg during and for 24 hours after alteplase
* For patients not receiving alteplase:
  + Permissive hypertension up to SBP 220 mm Hg and DBP 120 mm Hg for first 24 hours
  + Lowering BP by 15% reasonable if comorbid conditions require tighter control
* IV agents preferred for rapid titration:
  + Labetalol 10-20 mg IV push, may repeat q5-15 min
  + Nicardipine 5 mg/hr IV, titrate by 2.5 mg/hr every 5-15 minutes, maximum 15 mg/hr
  + Clevidipine 1-2 mg/hr IV, double dose every 2-5 minutes, maximum 21 mg/hr

#### tPA-Induced Angioedema

Angioedema is swelling involving the tongue, lips, or oropharynx due to localized nonpitting edema. It occurs in approximately 1-8% of patients receiving IV tPA for ischemic stroke. Those with a history of ACE inhibitor use appear to be at highest risk.

Management:

* Maintain airway - Awake fiberoptic intubation preferred over nasal intubation due to bleeding risk after tPA
* Discontinue tPA infusion
* Administer methylprednisolone 125 mg IV
* Administer diphenhydramine 50 mg IV
* Ranitidine 50 mg IV or famotidine 20 mg IV
* For severe angioedema, epinephrine 0.3 mg IM or nebulized
* Icatibant 30 mg subcutaneous (bradykinin B2 receptor antagonist) may also be considered

#### **Hemorrhagic Conversion**

Symptomatic ICH after IV tPA occurs in approximately 2-6% of treated patients. Risk factors include older age, stroke severity, glucose >200 mg/dL, delayed time to treatment, and early CT hypodensity.

Management within 24 hours of tPA:

* Stop tPA infusion immediately
* Emergent head CT
* INR, PTT, platelets, fibrinogen level
* Cryoprecipitate 10 units IV for fibrinogen <150 mg/dL
* Tranexamic acid 1 g IV over 10 minutes or aminocaproic acid 4-5 g IV over 1 hour
* Consider prothrombin complex concentrate if on warfarin with elevated INR
* Neurosurgery and hematology consultations
* Supportive care - blood pressure, glucose, and temperature management

Other Therapies

* Antiplatelets:
  + Aspirin 160-325 mg within 24-48 hrs of onset
  + Not recommended in hemorrhagic stroke
  + Delay 24 hrs after alteplase due to hemorrhage risk
  + Dual antiplatelet therapy (aspirin + clopidogrel) may have benefit in minor strokes if used short-term (21-30 days)
* Glucose control:
  + Treat hyperglycemia >180 mg/dL to limit neuronal injury
  + Continuous insulin infusion protocol if persistent hyperglycemia
  + Provide dextrose-containing IV fluids to avoid hypoglycemia
* Temperature management:
  + Treat fever >38°C aggressively to avoid exacerbating injury
  + Antipyretics, cooling blankets, cooling catheter systems
  + Avoid hypothermia <36°C
* DVT prophylaxis:
  + Intermittent pneumatic compression devices
  + Early mobilization
  + Subcutaneous heparin or LMWH when stable
  + Avoid enoxaparin for 24 hrs after alteplase
* Nutrition:
  + NPO until dysphagia screening
  + Enteral feeding if needed - NG tube, PEG tube
  + Monitor hydration status

### ****Key Guidelines and Evidence****

| **Guideline Recommendations for Acute Ischemic Stroke** | **Level of Evidence** | **Strength of Recommendation** |
| --- | --- | --- |
| IV alteplase 0.9 mg/kg (max 90 mg) if onset <3 hrs | A | I |
| IV alteplase 0.9 mg/kg (max 90 mg) if onset 3-4.5 hrs | B-R | I |
| Tenecteplase administered as a 0.4-mg/kg single IV bolus has not been proven to be superior or noninferior to alteplase but might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranialocclusion. | B-R | IIb |
| 1. Patients eligible for IV alteplase should receive IV alteplase even if EVTs are being considered. | A | I |
| 8. In selected patients with AIS within 6 to 24 hours of last known normal who have LVO in the anterior circulation and meet other DAWN eligibility criteria, mechanical thrombectomy is reasonable. | B-R | IIb |
| BP should be maintained <180/105 mmHg for at least the first 24 hours after IV alteplase treatment. | B-NR | I |
| IV alteplase 0.9 mg/kg (max 90 mg) if onset <3 hrs | A | I |
|  |  |  |

Level of Evidence:  
A = RCTs  
B = Single RCT or nonrandomized studies  
C = Expert opinion, case studies

Strength of Recommendation:  
I = Benefit >>> Risk  
IIa = Benefit >> Risk  
IIb = Benefit ≥ Risk  
III = No benefit or harm

Landmark Trials:

* NINDS rt-PA Stroke Trial - established efficacy of IV tPA within 3 hours
* ECASS III - expanded window for IV tPA to 4.5 hours
* Multiple trials culminating in HERMES meta-analysis - demonstrated benefit of endovascular thrombectomy up to 24 hours from onset in select patients

**Clinical Scenarios**

**Scenario 1**

* SB is a 62-year-old male with a history of atrial fibrillation on apixaban who awoke this morning with left-sided weakness and difficulty speaking. His symptoms began approximately 90 minutes prior to ED arrival. His NIHSS is 11. BP is 166/88 mm Hg and glucose is 118 mg/dL. Head CT shows no hemorrhage or extensive hypodensity. Which therapy should SB receive?

Scenario 1 Answer and Explanation

* SB is a candidate for IV alteplase since he meets inclusion criteria: symptoms onset within 4.5 hours, no contraindications like anticoagulant use or bleeding risks, and NIHSS >5. SB's BP is slightly elevated but does not require lowering prior to alteplase. He should receive 0.9 mg/kg IV alteplase over 1 hour following standard protocol.

**Scenario 2**

* RN is a 58-year-old female who awoke 5 hours ago with sudden right arm and facial weakness. On examination, she has dysarthria and right hemiplegia with NIHSS 18. Head CT shows a small hypodensity in the left MCA territory concerning for early infarct but no hemorrhage. CTA identifies a proximal left MCA occlusion. RN's glucose is 132 mg/dL and BP 142/78 mm Hg. She takes atorvastatin and metoprolol at home. What is the next best step in management?

Scenario 2 Answer and Explanation

* Although RN is outside the IV thrombolysis window, she has a large vessel occlusion on CTA and is within 24 hours of onset. She is a candidate for mechanical thrombectomy which could still improve outcomes. IV alteplase is not recommended due to extended time window but thrombectomy should be pursued urgently.

**Acute ischemic stroke Summary**

Acute ischemic stroke is caused by an arterial blockage restricting blood flow to the brain, resulting in infarction. Rapid diagnosis, blood pressure management, and urgent restoration of perfusion via thrombolysis and/or thrombectomy are critical. Antiplatelets have a delayed role. Anticoagulants are relatively contraindicated early after ischemic stroke given increased hemorrhage risk. Pharmacists play a key role in the hyperacute management and secondary prevention of ischemic strokes.

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