

Treatment of Acute Ischemic Stroke

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Editor's Note: This article continues a series of special contributions addressing state-of-the-art techniques, topics, or concepts. State-of-the-art articles will be featured in *Annals* on a regular basis in the next several volumes.

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Acute ischemic stroke is the third leading cause of death in the United States and the leading cause of adult disability. The direct and indirect costs of stroke care exceed \$51 billion annually. In 1996, the US Food and Drug Administration approved the first treatment for acute ischemic stroke, intravenous tissue plasminogen activator. Later that year, the National Institute of Neurologic Disorders and Stroke (a branch of the National Institutes of Health) convened a consensus conference on the Rapid Identification and Treatment of Acute Ischemic Stroke, setting goals for stroke care in the United States. Since then, it has become imperative that emergency physicians understand the pathophysiology of stroke, the basis and rationale for treatment, and the therapeutic approaches. This article reviews the state of the art of acute stroke treatment, its foundation, as well as its future.

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INTRODUCTION

The US Food and Drug Administration (FDA) approved intravenous tissue plasminogen activator (tPA) as the first treatment for acute ischemic stroke in June 1996. Since then, stroke has been in the forefront of discussion not only because of this new treatment but also because it is a major and growing health problem in the United States.¹ Stroke is a medical emergency that requires rapid initial evaluation and management to decrease its impact on patients and on society.² Other therapies are being developed that may also require rapid emergency department evaluation and treatment.³

The National Institute of Neurologic Disorders and Stroke (NINDS) defines the term "stroke" as a sudden loss of brain function resulting from an interference with the blood supply to the brain. It limits stroke to an acute vascular phenomenon that includes both ischemic strokes

and hemorrhagic strokes. Acute ischemic stroke makes up the majority (85%) of the annual 600,000 strokes in the United States, with a mortality rate of 20% to 50%, making it the third leading cause of death. Disability is the major sequela of stroke with 4.4 million survivors, 70% of whom do not return to gainful employment even 7 years after the stroke. Direct and indirect costs for stroke care in the United States exceed \$51 billion per year.¹

This article reviews the pathophysiology of acute ischemic stroke, its diagnosis, special issues in acute supportive care, acute primary therapy, and future directions.

PATHOPHYSIOLOGY OF ACUTE ISCHEMIC STROKE

Acute vascular occlusion is the central event in acute ischemic stroke precipitating the primary injury by limiting the flow of oxygen and glucose to a region of the brain. The occlusion is rarely complete. The residual cerebral blood flow (CBF) depends on the degree of obstruction and the availability of collateral flow. Because the brain does not store energy, it relies on a continuous supply of nutrients to meet its metabolic demands. Ultimately, the amount of injury is proportional to the duration and severity of the ischemia.⁴

Normal CBF is approximately 50 to 60 mL/100 g of tissue per minute but varies in different regions of the brain. The oxygen extraction fraction is approximately 50%, and the glucose extraction fraction is about 30%.⁵ As the amount of flow diminishes, the brain compensates by local vasodilatation, opening of collaterals, and increasing the fraction of extracted oxygen and glucose.⁶ When CBF is reduced below 50% of normal, synaptic transmission stops and electrical silence ensues, thereby decreasing cerebral energy use by 50%. Further decline in CBF results in membrane and ionic gradient failure, leading to a cascade of events that result in cell death.

In the area of ischemia, there is a central core with marked reduction in CBF and a surrounding area of marginal blood flow called the "ischemic penumbra."⁷ The CBF in the core is usually below 25% of normal. The CBF in the penumbra is 25% to 50% of normal, which is sufficient to preserve energy metabolism and to maintain tissue viability for a period of hours. Autoregulation is lost in the area of ischemia. The ischemic area becomes perfusion-dependent, and any decrease in systemic blood pressure can extend the area of ischemia and infarction.

The core is characterized by pannecrosis as a result of rapid depletion of energy stores leading to anaerobic metabolism, lactic acid accumulation, and acidosis.

Energy-dependent membrane ion pumps fail causing loss of normal ion gradients and membrane depolarization. There is an uncontrolled release of large presynaptic stores of excitatory amino acids, primarily glutamate and aspartate, that open calcium channels such as the N-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) channels. This excitotoxic response results in further membrane depolarization with calcium, sodium, and chloride influx while large intracellular potassium stores leak out. Intracellular calcium acts to activate a series of destructive cellular enzymes (proteases, endonucleases, phospholipases, and nitric oxide synthetase) while releasing more calcium from intracellular stores. This occurs in an acidotic medium (pH 6.5 to 6.9) that accelerates free radical formation, activates pH-dependent endonucleases, and further alters intracellular calcium metabolism. Elevated plasma glucose levels contribute to the development of acidosis by fueling anaerobic metabolism resulting in increased lactic acid production.⁸ Phospholipases attack the cell membrane releasing arachidonic acid, free radicals, and triggering an inflammatory cascade. A series of mediators including cytokines, interleukins, tumor necrosis factor, and platelet activating factor are produced. These begin the process of chemotaxis of neutrophils and macrophages, and platelet activation, leading to microvascular occlusion. Reperfusion and cellular infiltration may further exacerbate the inflammatory response. It begins within 1 hour, peaks in 12 hours, and lasts about 48 hours.⁹ Within the first hour, the most severe areas of ischemia progress to infarction and begin to spread outward to adjacent areas.

In the penumbra, there is moderate ischemia. Gradations of residual blood flow exist, but cellular membrane integrity and function is preserved. The penumbra becomes electrically silent within minutes of the initial vascular occlusion. Over time, this area is recruited into the growing core as it infarcts. Its duration of viability depends on local factors including CBF and may last 6 to 8 hours or longer. Moderate ischemia produces a mild acidosis and a hyperpolarization of the cell membrane that acts to protect the cell. Intermittent waves of depolarization (spreading depressions) caused by excitatory amino acids and massive calcium influx^{5,6} occur in the penumbra. In an environment of limited CBF, these spreading depressions cause cellular injury and use large amounts of precious energy for repolarization. NMDA/AMPA channel antagonists can inhibit these peri-infarct waves of spreading depression and decrease their frequency. Prolonged periods of moderate ischemia in the penumbra facilitate de-

velopment of the delayed processes such as inflammation and apoptosis (programmed cell death).¹⁰

Therapy for acute ischemic stroke relies on the presence of brain tissue that is viable and salvageable. The core requires almost immediate reperfusion if it is to be saved. The penumbra, maintaining viability for a longer time, is a natural target for medical intervention.

CLINICAL TRIALS

Thrombolysis for acute ischemic stroke is a strategy that dates back to the 1950s. The first modern randomized trials, which involved intravenous streptokinase, failed. The Multicenter Acute Stroke Trial of Europe (MAST-E),¹¹ the Multicenter Acute Stroke of Italy (MAST-I),¹² and the Australian Streptokinase Trial (ASK)¹³ were stopped early because of increased early mortality and high intracerebral hemorrhage (ICH) rates. They used 1.5 million units of streptokinase over 1 hour started within 6 hours of onset of symptoms for the MAST trials and within 4 hours for the ASK trial. The MAST-I study attempted to study the effect of aspirin in addition to streptokinase. Heparin use was not controlled, and the dose of streptokinase was not determined by dose escalation trials. The ASK investigators prospectively divided patients into 2 groups, those treated in the 0- to 3-hour window, and those treated after 3 hours. They concluded that treatment with streptokinase within 3 hours of onset was safer than treatment after 3 hours, but it did not show clinical benefit over placebo. Currently, treatment with streptokinase is not warranted and no further trials of streptokinase are planned.

Acute ischemic stroke trials using intravenous tPA have been completed in Europe and in the United States. The European Acute Stroke Trial (ECASS)¹⁴ was a double-blind, randomized, placebo-controlled trial of intravenous recombinant tPA (rtPA; 1.1 mg/kg over 1 hour, 10% as a bolus, maximum 100 mg) where infusion began within 6 hours of symptom onset. Patients with severe neurologic deficits or initial computed tomographic (CT) scans with major signs of infarction involving more than one third of the middle cerebral artery distribution were to be excluded. Two analyses were performed. The intention-to-treat analysis included all patients entered into the trial, and the target population analysis was only for those that met the strict inclusion criteria. One hundred nine patients were excluded from the intention-to-treat population, most for CT violations (n=66), leaving 511 in the target population analysis. The mean time to treatment was 4.4 hours.

The mortality rate in the intention-to-treat analysis was greater for the rtPA group at 90 days (22.4% versus

15.8%, $P=.04$). The target population analysis also had a higher mortality with tPA, but it did not reach statistical significance (19.4% versus 14.8%, $P=.17$). Forty-eight percent of those treated with rtPA who had major signs of infarction on initial CT (n=31) died. The rate of large parenchymal ICH was significantly greater in the rtPA group in both analyses (intention to treat, 19.8% versus 6.5%; and target population, 19.4% versus 6.8%).

ECASS failed to demonstrate an improvement with tPA in functional outcome (90-day Barthel Index) (Table 1) in either population. The target population did show improvement in the median Rankin score, and 41% of the rtPA target population compared with 29% of the placebo target population was considered independent (Rankin score ≤ 2) at 90 days.

The authors concluded that rtPA therapy could improve outcome in a carefully selected subgroup of patients, especially those without major infarct signs on the initial CT scan. Treating patients who do not meet strict eligibility criteria carries a high risk of ICH or death. Thus, thrombolytic treatment within 6 hours of symptom onset was not recommended for general use because the subgroups may be difficult to identify.

In the United States, a series of trials funded by NINDS ultimately demonstrated the safety and efficacy of intravenous rtPA for acute ischemic stroke when started within 3 hours of symptom onset. The NINDS trials were preceded by 2 open-label dose ranging pilot studies and a pilot randomized trial.

The NINDS rtPA Stroke Trial¹⁵ was conducted at 8 centers (totaling 45 hospitals, 5 academic medical centers, and 40 community hospitals). It was conducted as 2 consecutive trials that were reported together as Part 1 and Part 2. These were double-blind, randomized, placebo-controlled trials of intravenous rtPA at 0.9 mg/kg (10% as

Table 1.

Stroke scales of long-term functional outcome used in recent studies.

Stroke Scale	Scoring	Description
Modified Rankin Scale	0 to 5-point scale	0: No symptoms; 4 to 5: severe disability Patients with scores ≤ 2 are considered functionally independent
Barthel Index	0 to 100 points	5 to 10 points are awarded for activities of daily living 95 to 100: Minimal or no disability; >65: functionally independent

a bolus, and a 1-hour infusion, 90 mg maximum) versus placebo that enrolled a total of 624 patients.

In Part 1, the primary purpose was to test drug activity at 24 hours; 3-month functional outcome data were also collected. There was no significant difference in the primary outcome measure between the rtPA group and the placebo group; 47% versus 39% of patients achieved a 4-point improvement on the National Institutes of Health–Stroke Scale Score (NIH-SSS) (Table 2) at 24 hours ($P=.21$). However, 17% of patients treated with tPA returned to normal or near-normal status (NIH-SSS 0, 1) at 24 hours compared with 3% of those treated with placebo. Three-month functional outcome data in Part 1 showed a strong and consistent improvement in the rtPA group with an absolute difference of 15% to 20% more patients attaining a favorable outcome at 3 months. The odds ratio (OR) of 2.1 (95% confidence interval [CI] 1.3 to 3.2; $P=.001$) favored treatment with rtPA.

Part 2 was the pivotal study that established long-term efficacy, with a primary end point of normal or near-normal function at 3 months. There was an absolute increase of 11% to 13% in the proportion of patients achieving this favorable outcome in the rtPA group compared with the placebo group (or a 24% to 35% relative increase). The OR for improvement with rtPA was 2.0 (95% CI 1.3 to 3.1) after adjusting for baseline differences in age, weight, and aspirin use. This positive effect was consistently present in subgroup analysis by age, baseline NIH-SSS, stroke subtype (lacunar, large-vessel, and cardioembolic), and aspirin use before treatment. The FDA considered the secondary (3-month) outcomes of Part 1 confirmatory evidence of long-term efficacy.

Symptomatic ICH (within 36 hours of stroke) occurred in 6.4% of the rtPA-treated patients and in 0.6% of placebo-treated patients ($P<.001$). The patients with symptomatic ICH had a higher median NIH-SSS at baseline than those without (20 versus 14). The rate of asymptomatic ICH was not statistically different (4.5% versus 2.9%). Despite the increased risk of ICH with rtPA treatment, and a 50% mortality rate associated with symptomatic ICH (in either placebo or rtPA group), the 3-month mortality rate was not different; 17% of rtPA-treated patients and 21% of the placebo-treated patients died within 3 months ($P=.30$).

The authors concluded that despite an increased risk of symptomatic ICH, treatment with rtPA provided a consistent benefit in functional outcome at 3 months without increasing mortality.

Attempts at demonstrating efficacy of intravenous tPA beyond the 3-hour window for acute ischemic stroke continued in the ECASS II trial¹⁶ and the Alteplase Throm-

Table 2.

NIH-SSS summary.

Categories and Point Assignments

1a. Level of consciousness

- 0: Alert
- 1: Drowsy
- 2: Stuporous
- 3: Comatose

1b. Level of consciousness questions (ask age and month)

- 0: Answers both correctly
- 1: Answers 1 correctly
- 2: Both incorrect

1c. Level of consciousness commands (close your eyes, make a fist)

- 0: Obeys both correctly
- 1: Obeys 1 correctly
- 2: Both incorrect

2. Best gaze

- 0: Normal
- 1: Partial gaze palsy
- 2: Forced deviation

3. Visual fields

- 0: No visual loss
- 1: Partial hemianopia
- 2: Complete hemianopia
- 3: Bilateral hemianopia

4. Facial paresis

- 0: Normal movement
- 1: Minor paresis
- 2: Partial paresis
- 3: Complete palsy

5-8. Best motor (repeat for each arm and each leg)

- 0: No drift
- 1: Drift
- 2: Some effort versus gravity
- 3: No effort versus gravity
- 4: No movement
- 9: Untestable

9. Limb ataxia (scored only if present)

- 0: Absent
- 1: Present in 1 limb
- 2: Present in 2 limbs

10. Sensory (pinprick)

- 0: Normal
- 1: Partial loss
- 2: Dense loss

11. Best language

- 0: No aphasia
- 1: Mild to moderate aphasia
- 2: Severe aphasia
- 3: Mute

12. Dysarthria

- 0: Normal articulation
- 1: Mild to moderate dysarthria
- 2: Unintelligible or worse
- X: Untestable

13. Neglect/Inattention

- 0: No neglect
- 1: Partial neglect
- 2: Complete neglect

Total NIH-SSS _____ (0 to 42)

*Numbers represent the point score assigned for each variable within the category.

bolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) trial¹⁷ using the 0.9-mg/kg dose. These trials had more ICH with tPA than with placebo, but no difference in mortality or functional outcome. Both studies failed to provide evidence to support using thrombolysis beyond the 3-hour window.

Ancrod, a selective defibrinogenating agent derived from the venom of the Malaysian pit viper, has been shown to improve outcome for patients with acute ischemic stroke.¹⁸ Ancrod works by lowering the fibrinogen level, thereby decreasing serum viscosity and increasing CBF. It also acts as an anticoagulant, preventing thrombus formation, while promoting thrombolysis by stimulating endogenous tPA release, inhibiting plasminogen activator inhibitor, plasmin inhibitor, and platelet function.

The Stroke Treatment with Ancrod Trial (STAT) was a double-blind, randomized, placebo-controlled trial of ancrod versus placebo within 3 hours of onset of symptoms. Ancrod was infused for 5 days and adjusted for a target fibrinogen level of 40 to 70 mg/dL. Forty-two percent of the patients in the ancrod group and 34% in the placebo group ($P<.05$) achieved functional independence at 90 days. Symptomatic ICH occurred in 5.2% with ancrod and 2.0% with placebo; the mortality rates were identical at 10%. Patients whose fibrinogen level decreased to too-low levels (<40 mg/dL) had a symptomatic ICH rate of 13%.

Aspirin, heparin, and low molecular weight heparin (LMWH) have been investigated as primary treatment in randomized trials. The International Stroke Trial (IST)¹⁹ investigated the use of aspirin alone, subcutaneous heparin alone (high-dose and low-dose), and both in combination compared with no treatment in an open trial involving 19,435 patients. IST showed that aspirin given within 48 hours and continued for 14 days prevented 11 recurrent strokes per 1,000 treated patients and caused 1 ICH per 1,000 treated patients, and 14 per 1,000 fewer patients were dead or dependent at 6 months. The Chinese Acute Stroke Trial (CAST)²⁰ was a placebo-controlled trial of aspirin given within 48 hours of onset and continued for 4 weeks in 21,106 patients. It showed a benefit with 13 fewer patients dead or dependent per 1,000 treated at hospital discharge. Patients who had been taking aspirin and were treated in the NINDS tPA Stroke Trial did not have a measurable increase in risk of ICH.²¹

In IST, treatment with heparin in the first 48 hours after acute ischemic stroke decreased the rate of pulmonary embolism and recurrent acute ischemic stroke, but increased bleeding complications and mortality related to ICH. The final result was that there was no difference in outcome with heparin in terms of 14-day mortality or death and disability at 6 months.

The Trial of ORG 10172 (danaparoid) in Acute Stroke Treatment (TOAST)²² versus placebo within the first 48 hours of acute ischemic stroke is the largest LMWH trial to date. It did not show any significant difference in favorable outcome at 3 months, mortality, or recurrence of stroke. There was an increased risk of major bleeding and ICH. In general, there is no proven benefit of heparin or LMWH in the treatment of acute ischemic stroke beyond that of prevention of deep venous thrombosis.

Clinical trials of intravenous neuroprotective agents have not been as successful as reperfusion agents.²³ Despite highly successful studies in animal models, translation into human trials has proved difficult. To date, none of the neuroprotective agents have shown efficacy in clinical outcome or in prolongation of the therapeutic window.

Intra-arterial thrombolysis for acute ischemic stroke is an attractive approach. Recent advances in catheter technology have made superselective infusion of a thrombolytic drug directly into the culprit clot possible. This provides delivery of the drug directly to the thrombus, thereby requiring lower doses, and possibly higher recanalization rates, more rapid thrombolysis, and fewer complications. However, it is a strategy that is highly technical and not widely available, requiring a longer time to initiation of treatment. Intra-arterial thrombolysis is used only in patients with a visible clot. Yet not all vascular occlusions can be visualized angiographically, especially those involving small penetrating arteries such as the lenticulostriate arteries, eliminating patients who may otherwise respond to intravenous therapy.

The only randomized, placebo-controlled, double-blind trials of intra-arterial therapy for acute ischemic stroke have been of recombinant pro-urokinase (r-pro-UK) in the Prolyse in Acute Cerebral Thromboembolism (PROACT) trials. PROACT I²⁴ was a pilot study that found greater recanalization with r-pro-UK than with placebo for proximal middle cerebral artery occlusions without a significant difference in symptomatic ICH rates. This led to a larger phase 3 trial.

PROACT II²⁵ enrolled 180 patients to evaluate the recanalization, safety, and efficacy of intra-arterial therapy within 6 hours of middle cerebral artery occlusions. Recanalization was clearly better with 9 mg of r-pro-UK infused directly into the proximal one third of the clot for 120 minutes than with placebo. TIMI grade 2 or 3 flow (partial or full perfusion) was established in 67% of the treated group ($n=108$) versus 17% of the placebo group ($n=55$).²⁶ Safety analysis did not reveal any difference in mortality (26% versus 24%), but there were more symptomatic ICHs within the first 36 hours with r-pro-UK (10% versus 2%). There was a clinical benefit at

90 days; 40% of the r-pro-UK group functioned independently compared with 25% of the placebo group ($P=.043$).

Intra-arterial thrombolysis has also been used in basilar artery occlusion.²⁷ Basilar artery occlusion often presents with bilateral sensory and motor findings combined with cranial nerve and cerebellar dysfunction. This can progress to the locked-in syndrome, stupor, and coma. Because of the devastating nature of this syndrome, which carries a mortality rate of up to 90%, it is important to recognize imminent basilar artery occlusion.²⁸ The clinical presentation of basilar artery thrombosis is often stuttering, and the deficit may not be maximal at onset. For intra-arterial thrombolysis, the time from onset of symptoms to lysis has been empirically extended out as far as 24 hours with reasonable success. Hacke et al²⁹ compared intra-arterial treatment with standard heparin treatment. Recanalization occurred in 19 of 43 patients treated with local intra-arterial urokinase. Fourteen of these patients survived, 10 with a favorable outcome. Eighty-six percent of patients with standard therapy died, as did all of those without recanalization. At this time, a randomized controlled trial of intra-arterial urokinase for basilar artery occlusion is under way in Australia. Until the results of this trial are available, patients with basilar artery occlusion could be considered for intra-arterial treatment on a compassionate basis.

A unique approach to recanalization combines the advantages of both the intravenous and intra-arterial approaches. This strategy allows patients to begin treatment as soon as possible with a lower dose of intravenous tPA (0.6 mg/kg over 30 minutes), followed by angiography and superselective intra-arterial therapy. If no occlusion is present at angiography, no further intra-arterial treatment is offered. Those without angiographically visible occlusion may have small-vessel disease and still receive intravenous treatment. The results of a pilot randomized trial³⁰ were sufficiently encouraging to warrant further investigation of this approach.

PRINCIPLES OF EMERGENCY MANAGEMENT

Diagnosis

Acute ischemic stroke occurs at a median age of 65 years, just at the beginning of the retirement years. It is characterized by a sudden onset of focal neurologic deficit, which is generally maximal at the time of onset, but can wax and wane over the initial few hours. Approximately 5% of patients with acute ischemic stroke present with a seizure, and up to 30% have a headache.³¹ Those at greatest risk often have risk factors similar to those for coro-

nary artery disease, or a history of transient ischemic attack (TIA), previous stroke, or atrial fibrillation. The time of onset of the stroke is a critical piece of information in establishing eligibility for thrombolytic therapy. Out-of-hospital care providers can be very helpful in determining the time of onset especially if they transport a family member or witness with the patient.

A general examination should be undertaken to assess the overall condition of the patient and to prevent omission of other associated problems that may be life-threatening. Attention should be directed to blood pressure in both upper extremities, symmetry of pulses, and signs of trauma.

The neurologic examination is the cornerstone of determining whether a focal neurologic deficit in a characteristic vascular distribution exists. To provide for uniform assessments that are consistent and reproducible between examiners, various stroke severity scales have been developed. The National Institutes of Health Stroke Scale (Table 1) is a 42-point standardized scale that was developed for the NINDS rtPA Stroke Trial and is currently in common use as an indicator of the severity of neurologic dysfunction.³² It is easy to learn and has good interrater and intrarater reliability.³³ Low NIH-SSs of 0 or 1 indicate a normal or near-normal examination. Scores of 1 to 4 indicate minor strokes though certain syndromes (such as global aphasia) may be severely disabling while having a low NIH-SSS. Scores of 5 to 15 generally indicate a moderate stroke, 15 to 20 a moderately severe stroke, and more than 20 a severe stroke. It also allows for accurate documentation of stroke severity for outcome analysis or comparison of therapeutic interventions but does not replace the conventional neurologic examination. Functional stroke scales (Table 1) are used to assess a patient's functional capacity after stroke but are of limited use in the acute setting. The severity of the stroke should be judged in relation to its impact on the specific individual patient and not by the score alone.

The differential diagnosis of stroke includes seizures, trauma, structural central nervous system abnormalities, vascular disorders, metabolic abnormalities, infections, and other neurologic conditions such as Bell's palsy, complex migraine, and dural sinus thrombosis. These disease processes can be quickly distinguished from a stroke by history of abrupt onset, a physical examination demonstrating a focal neurologic deficit in a vascular territory, a CT scan of the brain, and a basic laboratory evaluation.

TIAs are exact mimics of acute ischemic stroke. These brief episodes of focal neurologic deficit resolve (by definition) in less than 24 hours and do not cause tissue in-

fraction or any residual neurologic deficit. The majority (80%) of TIAs last only 7 to 10 minutes, but focal deficits lasting as short as 1 hour may cause permanent infarction. Patient observation during the initial evaluation period can help distinguish a TIA from a stroke. TIAs carry a 30% 5-year risk of stroke.

Basic diagnostic studies should be included in the initial evaluation of patients with an acute stroke. The American Heart Association recommends an ECG, chest radiograph, CBC count, platelet count, partial thromboplastin time, prothrombin time, serum electrolytes, and glucose level.³⁴ Other studies should be ordered as indicated.

Noncontrast CT scanning of the brain is the mainstay of emergency imaging of acute stroke patients. It is widely available, rapid, and reliable. It is the most reliable method for diagnosing ICH with a sensitivity of nearly 100%. Fresh blood is hyperdense (white) on the CT scan. It has a density of 50 to 85 Hounsfield units (HU), whereas calcifications have a density of approximately 120 HU (70 to 200 HU) allowing for differentiation from other hyperdense structures.³⁵ Rare false-negative scans can occur in patients with an extremely low hematocrit (<20%) when intracranial blood may be isodense with brain tissue.

In the hyperacute phase of stroke, CT scanning generally does not show signs of acute ischemia. Its sensitivity for an acute stroke depends on the time of imaging from onset of symptoms. Within 3 hours of onset, the sensitivity is low (30%), within 24 hours it improves to more than 60%, and to 100% by 7 days.³⁶ Early signs of ischemia can be seen on CT scans but should prompt a reevaluation of the time of onset of symptoms, especially in candidates for intravenous thrombolysis.

The CT scan can provide valuable prognostic information when early findings are present in the hyperacute phase. These findings are subtle but can be seen as early as 2 hours from onset of symptoms. They are thought to reflect cytotoxic edema with an increase in intracellular water content. Effacement of sulci or ventricles, blurring of the basal ganglia, mass effect, and loss of the normal gray-white junction especially in the insula (the cortex beneath the sylvian fissure), or loss of the insular ribbon³⁷ may be seen on the initial study. Later, hypodensity is visible and is thought to be a marker of tissue destined to become necrotic.

Major early ischemic findings, primarily hypodensity, involving more than 33% of the middle cerebral artery territory portend a poor prognosis and an increased risk of ICH with thrombolytic treatment according to the ECASS investigators.³⁸ One third of the middle cerebral

artery territory has been defined as involving 2 of the following 4 areas: frontal, parietal, or temporal lobes, and the basal ganglia.¹⁷ In the ECASS I trial, 8.4% of the 620 patients presented with early ischemic signs within 6 hours of symptoms onset. They had a 67% rate of severe disability or death when treated with tPA and a 77% rate of severe disability or death when treated with placebo.³⁹ In the NINDS trial, clear hypodensity on baseline CT scan of any size increased the risk of ICH (OR 7.8, 95% CI 2.2 to 27.1). These patients still responded to tPA without an increased risk of severe disability or death (56% with tPA, 52% with placebo).²¹

Initial CT scan of the acute stroke patient may also reveal a hyperdense middle cerebral artery. This is thought to be caused by fresh clot or embolus in the stem of the middle cerebral artery. It is often associated with other signs of severe ischemia on CT scan, larger neurologic deficits, and a poor prognosis. It is an extremely specific sign of middle cerebral artery occlusion (85% to 100%) but it is not very sensitive (25% to 69%). Because other signs and symptoms are associated with hyperdense middle cerebral artery, it has not been shown to have any independent prognostic value for outcome or for response to tPA.^{21,40}

Recent advances in CT technology (helical CT) have allowed for the development of additional CT imaging modalities. Adjuncts to the emergency evaluation of stroke patients such as CT angiogram,⁴¹ perfusion CT,⁴² triphasic helical CT,⁴³ and xenon CT⁴⁴ are currently under investigation to determine their role in patient management.

Magnetic resonance imaging (MRI) is becoming more important in the evaluation of the acute stroke patient. Although conventional MRI has little advantage over noncontrast CT imaging for the early evaluation of acute ischemic stroke,³⁶ it does provide better contrast resolution and multiplanar imaging without the use of ionizing radiation. Conventional MRI can show early edema and mass effect better than CT scanning, and is useful for imaging the posterior fossa and brainstem where artifact from bone renders CT scanning of limited value. The ability of conventional MRI to detect ICH is limited and depends on the stage of hematoma evolution. Therefore, in the acute phase, ICH is more difficult to detect on conventional MRI than on CT scan.³⁵ MRI requires 5 to 10 minutes to generate a set of images and any patient movement can distort not just one but all of the images. Further, patient management can be difficult in the magnet, posing problems with monitoring and claustrophobia. Patients with any ferromagnetic objects in their body are not eligible for any type of MRI.

New MRI technology called echo-planar MR imaging (EPI) uses high-speed pulsations and can acquire data for image production in milliseconds, scanning the entire brain in 5 to 10 seconds.⁴⁵ It can produce functional imaging through diffusion-weighted imaging and perfusion imaging techniques. Diffusion-weighted imaging detects diffusion of water molecules over time. In acute ischemic stroke, edema restricts water movement. Lesions seen with diffusion-weighted imaging are thought to represent the ischemic core of the stroke.⁴⁶

Perfusion imaging requires gadolinium contrast and provides an image of relative cerebral blood volumes. Perfusion imaging provides information about areas of hypoperfusion. The combination of the diffusion-weighted and perfusion imaging is thought to provide information about the core (diffusion-weighted imaging), the ischemic penumbra (perfusion imaging), and the amount of reversible ischemia. Additionally, MR angiography allows visualization of occlusions in the neck and major intracranial arteries. In the future, this modality may assist clinicians in assessing the pathophysiologic state of patients with acute ischemic stroke in real time and help determine appropriate time windows or treatment strategies on an individual basis.⁴⁷

Noncontrast CT scan of the brain remains the imaging technique of choice for acute ischemic stroke because it is readily available, fast, reliably visualizes ICH, and provides prognostic information to assist in the treatment of acute stroke patients.

Acute supportive care

General supportive care should be instituted for all patients with stroke to ensure maximal perfusion and oxygenation of the brain regardless of the underlying pathology (subarachnoid hemorrhage, ICH, or ischemic stroke). Emergency physicians are well versed in this approach. Some aspects of care deserve special attention as they affect every stroke patient.

Hypertension is common in acute stroke and should be treated cautiously if at all.^{34,48} In most cases, hypertension should not be treated at all during the acute phase of a stroke as it resolves spontaneously over hours to days.^{49,50} Exceptions include certain patients with intracranial hemorrhage and hypertension that develops during or soon after rtPA administration for ischemic stroke. Consensus on the exact management of hypertension in acute stroke does not exist. The American Heart Association recommends treating hypertension in the acute stages of stroke if the systolic blood pressure is more than 220 mm Hg, or if the mean arterial pressure is more

than 130 mm Hg.³⁴ The National Stroke Association recommends treating hypertension in the acute stages of stroke if the blood pressure exceeds 220/115.⁵¹ If patients have signs or symptoms of other end organ damage, such as an acute myocardial infarction, congestive heart failure, or an aortic dissection, the blood pressure should be treated accordingly. For patients with ischemic stroke undergoing evaluation for thrombolysis, the American Heart Association guidelines recommend that the blood pressure not exceed 185/110 mm Hg at the time of treatment.⁵⁰ The blood pressure should not be aggressively treated to bring it into the normal range, but mild forms of drug therapy are acceptable (Table 3). Simple maneuvers such as elevation of the head of the bed may help control hypertension by increasing the cerebral venous drainage.

Hypotension can dramatically decrease the cerebral perfusion pressure and cerebral blood flow, extending the area of infarction.⁵² Hypotension should be viewed in the context of the past medical history, understanding that for patients with long-standing hypertension, the autoregulatory curve is shifted to a higher blood pressure range. During an acute stroke, perfusion of ischemic areas is directly related to the mean arterial pressure. Hypotension should be evaluated and treated aggressively with intravenous fluids, inotropic agents, or vasopressors as

Table 3.
Blood pressure guidelines.

Pretreatment blood pressure guidelines

If the blood pressure is >185/110 mm Hg, the blood pressure may be treated with nitroglycerin paste or 1 to 2 doses of intravenous labetalol, 10 to 20 mg each. If these do not reduce blood pressure to <185/110 mm Hg over 1 h, the patient should not be treated with rtPA.

During and after treatment

For systolic blood pressure 180 to 230 mm Hg or diastolic blood pressure 105 to 120 mm Hg on 2 readings 5 to 10 min apart, use:

1. Labetalol, 10 mg intravenously over 1 to 2 min, repeat or double every 10 to 20 min; total maximum dose 150 mg
2. Monitor blood pressure every 15 min

For systolic blood pressure >230 mm Hg or diastolic blood pressure 121 to 140 mm Hg for 2 or more readings, for at least 2 readings 5 to 10 min apart:

1. Use labetalol, 10 mg intravenously over 1 to 2 min, repeat or double every 10 min, to a maximum of 150 mg
2. Monitor blood pressure every 15 min
3. If response unsatisfactory, use sodium nitroprusside with continuous blood pressure monitoring

For diastolic blood pressure >140 mm Hg for 2 or more readings, 5 to 10 min apart, use:

1. Sodium nitroprusside
2. Monitor blood pressure every 15 min

Avoid hypotension

necessary to maintain organ perfusion and prevent extension of the infarct.

ECG changes such as T-wave inversions occur in 15% to 75% of acute stroke patients.⁵³ Cardiac rhythm and function can be affected by an acute stroke, especially hemispheric strokes that involve the insula, although it is most commonly associated with subarachnoid and intracerebral hemorrhages. Cardiac disturbances are the result of increased sympathetic tone, catecholamine release from the brain, and decreased parasympathetic tone. Treatment of arrhythmias should be instituted if there is any hemodynamic compromise.

Hypervolemic hemodilution may improve cerebral blood flow by decreasing serum viscosity and increasing cardiac output.⁵⁴ There is no evidence that the addition of colloid volume expanders such as albumin, hydroxyethyl starch, or low molecular dextran improve clinical outcome, or are better than isotonic volume expansion. Elderly patients who are prone to dehydration, who use diuretics, or who may present with unknown downtimes may require isotonic fluids. Hypotonic fluid (5% dextrose [D₅W]) should be avoided as it may contribute to cerebral edema.³⁴

Patients with hyperglycemia at the time of the acute event, whether previously known to be diabetic or not, have worse outcomes.⁵⁵ The influence of glucose is related to continued anaerobic metabolism in ischemic tissues with production of lactic acid. Residual blood flow to the ischemic area is a requisite for glucose mediated injury. Glucose levels do not affect outcomes after lacunar infarcts as they involve end arteries.⁵⁶ Insulin acts as a neuroprotective agent by decreasing blood glucose levels and through direct interaction with ischemic tissue. Therefore, intravenous fluids should not include glucose, and hyperglycemic patients should be treated with insulin to achieve euglycemia.

Elevations in brain temperature have also been shown to worsen cerebral ischemia and are associated with increased stroke severity, infarct size, mortality, and worse outcome. In a study of 390 acute ischemic stroke patients, each temperature elevation of 1°C increased the risk of poor outcome by a factor of 2.2.⁵⁷ Elevations in temperature have the greatest effect and are most important in the first 24 hours after stroke. Hyperthermia is easy to underestimate, as brain temperature is higher than core body temperature and varies within regions of the brain.⁵⁸ Studies of induced hypothermia in acute ischemic stroke have been encouraging but are not definitive.³⁴ At this time, fever of any degree, even mild hyperthermia, should be treated with antipyretics (acetaminophen) and its cause should be investigated.

Seizures are a serious complication of acute stroke. They occur in approximately 5% of patients and may be related to involvement of the cerebral cortex or very large strokes. Seizures in the acute stroke patient should be managed in the same manner as any other seizure would be managed in the ED. Phenytoin should be administered after the seizure, but no evidence exists to support prophylactic use in acute ischemic stroke.^{34,51}

Oxygen delivery and oxygenation should be optimized. Additional supplemental oxygen for those who are not hypoxic has not been shown to improve outcomes in acute ischemic stroke.

Finally, aspirin should be given in the early stages of stroke unless the patient is a candidate for thrombolytic therapy, in which case it is prohibited for the first 24 hours only.

Acute primary treatment

Primary treatment of acute ischemic stroke currently consists of reperfusion through intravenous thrombolysis. Intra-arterial thrombolysis with r-pro-UK²⁷ and treatment with anicrod¹⁸ have been shown to be safe and effective in initial trials but are not approved by the FDA. The treatment of basilar artery occlusion with intra-arterial therapy appears to be a reasonable option even beyond the 3- to 6-hour window, although this therapy is yet unproven. Neuroprotective agents are still under investigation. Because intravenous tPA is the only FDA-approved primary therapy at this time, it is the focus of the remainder of this discussion.

Appropriate patient selection for intravenous thrombolysis is founded on close adherence to the inclusion and exclusion criteria that have been adapted from the experience gained in the major thrombolytic trials (Table 4). The inclusion and exclusion criteria for thrombolysis are listed in Table 5. They are similar in many respects to those used for thrombolysis for acute myocardial infarction. Their intent is to differentiate those patients who do not have a stroke, have transient neurologic deficits, or could be harmed by therapy. These criteria are generally self-explanatory.

The most difficult part of the inclusion criteria is accurate determination of the time of onset of symptoms as infusion must start within 3 hours. The critical first step is to understand when the patient's condition was last known to be "normal." Patients who awaken with their symptoms are considered to have an onset when they went to sleep. Emergency medical services (EMS) personnel can assist by determining the time of onset or transporting family members with the patient to the hospital.

Some of the exclusion criteria are absolute contraindications (ie, ICH on initial CT scan or blood pressure >185/110 mm Hg at time of treatment), whereas others are warnings. For example, patients with seizure at symptom onset may suffer an injury that would increase their risk of ICH or may present with Todd's paralysis. But if a patient has a witnessed seizure in front of the health care team during the early phases of the stroke without injury, he or she should not be excluded. In fact, this may be an indication of a relatively large amount of ischemic penumbra that is still viable.⁵⁹ Patients with a TIA generally have dramatic and rapid improvement (within an hour), whereas many stroke patients have waxing and waning symptoms that may improve but significant deficits persist. The period from "door to needle" is sufficient to understand this difference. In the NINDS trial, only 2% of placebo patients had an NIH-SSS of 0 (normal) at 24 hours, thereby technically meeting the definition of a TIA.

Table 4.

Inclusion and exclusion criteria for use of thrombolysis in acute ischemic stroke.

Inclusion criteria

1. Ischemic stroke with a measurable defect on NIHSS
2. Clearly defined time of onset within 3 h of the start of treatment
3. Age >18 y

Exclusion criteria

Contraindications

1. Evidence of intracranial hemorrhage on pretreatment CT scan
2. Clinical presentation consistent with subarachnoid hemorrhage, even with a normal CT scan
3. Known arteriovenous malformation or aneurysm
4. Prior intracranial hemorrhage
5. Active internal bleeding
6. Known bleeding diathesis including but not limited to: platelet count <100,000/mm³; prothrombin time >15 seconds, international normalized ratio >1.7, or current use of oral anticoagulants; use of heparin within 48 h and prolonged partial thromboplastin time
7. Systolic blood pressure >185 mm Hg, or diastolic blood pressure >110 mm Hg on repeated measurement at the time treatment is to begin (aggressive measures should not be used to reduce blood pressure to these limits)
8. Within 3 mo of: intracranial surgery, serious head trauma, or previous stroke
9. Major surgery within 14 d
10. Pregnancy
11. Post-myocardial infarction pericarditis

Warnings

1. Rapid improvement of neurologic signs
2. Mild stroke or isolated neurologic deficits
3. Gastrointestinal or genitourinary bleeding within 21 d
4. Recent lumbar puncture
5. Recent arterial puncture at noncompressible site
6. Blood glucose level <50 or >400 mg/dL
7. Seizure at same time stroke observed

Patients with mild strokes should not be treated as they generally do well. But there is no cutoff on the NIHSS below which patients should not be treated, as certain stroke syndromes (ie, aphasia) can be devastating without producing a high score.

The ECASS investigators found that patients with more than 33% of the middle cerebral artery territory involved with early signs of ischemia on the baseline CT scan who received tPA were at increased risk for ICH and early death (67% with severe disability or death).⁴⁷ This is a controversial finding because it is based on a 6-hour treatment window. The American Heart Association advises that patients with initial CT findings of recent major infarction should not be treated with tPA,⁵⁰ whereas the National Stroke Association recommends caution and that its use be weighed against the anticipated benefit.⁵¹ Most often, early signs of cerebral edema indicate that the time from onset is longer than 3 hours.

Despite the demonstrated efficacy of the inclusion and exclusion criteria, questions still remain about patient selection. If patients at increased risk for ICH could be excluded or patients who respond the best or least to treatment could be identified, then the safety and efficacy of this approach might be enhanced. In an effort to address these issues, the NINDS investigators conducted 2 analyses.

The first analysis attempted to identify pretreatment patient characteristics associated with an increased risk of ICH²¹ related to tPA. Two factors were found to be independently associated with an increased risk of ICH: the severity of the stroke and clear signs of infarction (hypodensity or mass effect) on baseline CT scan. Patient age was not found to be an independent risk factor for ICH in this analysis.

The severity of stroke was categorized by the baseline NIH-SSS (Table 5). Patients with baseline NIH-SSS less

Table 5.

Risk of symptomatic ICH by baseline NIH-SSS in the NINDS tPA Stroke Trial.

NIH-SSS	Patients With Symptomatic ICH (%)
1-5	2
6-10	3
11-15	5
16-20	4
<20	17

than 10 had a 3% risk of ICH, whereas those with NIH-SSSs higher than 20 had a 17% risk. Despite this, patients treated with tPA and an NIH-SSS higher than 20 had an OR of 4.3 (95% CI 1.6 to 11.9) in favor of full recovery and a lower risk of being severely disabled or dead (69% versus 76%, difference not significant) at 3 months. Therefore, those with large strokes should still be considered for treatment.

In the NINDS trial, 5% of patients had clear signs of infarction (hypodensity or mass effect) on baseline CT scan.²¹ Initial CT findings were not further categorized into greater than or less than 33% of the middle cerebral artery territory. Thirty-one percent (n=5) of those with hypodensity or mass effect on the baseline CT scan had a symptomatic ICH, compared with 5% (n=15) of those without these signs. Nevertheless, those treated with tPA who had edema or mass effect on baseline CT scan still had a better outcome: 25% versus 16% returned to normal (OR 3.4, 95% CI 0.6 to 20.2). The overall efficiency of these 2 factors in predicting ICH was poor at 57% (sensitivity 60% and specificity 56%).

The second analysis attempted to understand what factors influenced response to tPA therapy and what factors predicted 3-month outcome.⁶⁰ A subgroup of patients (based on pretreatment characteristics) that did not respond to tPA therapy could not be identified. Treatment with tPA was independently associated with the likelihood of a favorable outcome (NIH-SSS of 0 or 1) at 3 months (OR 2.02, $P=.0001$). There was no evidence to withhold therapy from any subgroup; sicker patients still may benefit. The clinical benefit of tPA is above and beyond the ICH rate so that complications should not be subtracted from its degree of benefit.

Thrombolytic therapy is similar in risk to that of other standard treatments of acute ischemic stroke. For example, the perioperative complication rate (death or stroke) for carotid endarterectomy (on symptomatic high-grade stenosis) is approximately 5% to 6%^{61,62} (requiring 11 surgeries to prevent 1 stroke). The risk of a major hemorrhagic complication from anticoagulation with warfarin (Coumadin) for chronic atrial fibrillation is 1.5% per year, and 33 patients need to have anticoagulation annually for every stroke prevented.^{61,63} These risks are considered worthwhile because of the devastating effects of acute ischemic stroke. The risk of symptomatic ICH with lytic therapy is 6.4%, and 8 patients need to be treated to return 1 person to full function. Furthermore, intravenous tPA is cost-saving by decreasing the length of hospital stay, discharges to rehabilitation facilities, and discharges to nursing homes.⁶⁴

In summary, patients should be selected based on the inclusion and exclusion criteria of the National Stroke Association,⁵¹ American Heart Association,⁵⁰ or American Academy of Neurology.⁶⁵ Patients with signs of early ischemia or severe strokes (NIH-SSS >20) may be acceptable candidates based on individual considerations despite higher rates of ICH. Patients with signs of edema or mass effect on the initial CT scan should have the time of onset of symptoms confirmed. If the time of onset is correct, they may represent a subgroup with more severe ischemia and an increased risk of ICH.

The treatment of patients with tPA can be divided into 3 phases: the out-of-hospital phase, the ED phase, and the hospital phase. First, the patients and their families should be aware of the signs and symptoms of stroke. The fastest and safest way to get to the hospital for acute treatment is to activate the 911 system.⁶⁶

The EMS dispatcher should suspect a stroke based on the initial call and dispatch an appropriate unit. Once on the scene, the EMS personnel must evaluate the patient, provide critical lifesaving interventions, notify the receiving hospital, and transport the patient. Prenotification allows preparations to take place while en route. Transporting a family member or witness with the patient facilitates confirmation of the time of onset of symptoms. EMS personnel should be very sensitive to identify all potential candidates using the inclusion criteria.

The ED role is to be very specific in candidate selection by assessing the exclusion criteria as well as confirming the inclusion criteria. The NIH-SSS confirms and quantifies the extent of the stroke, facilitates discussions about risks and benefits, improves communication with colleagues, and allows for accurate reassessment of progress. Critical laboratory evaluation includes CBC count with platelets, blood glucose, and partial thromboplastin time or prothrombin time. The prothrombin time/partial thromboplastin time determinations are not mandatory when there is no history of anticoagulant use or no history of bleeding or bleeding disorders.

An emergency CT scan is performed to exclude those with hyperdensity consistent with intracranial bleeding. Hypodensity, edema, or mass effect may be seen with early infarction, but should lead to a reevaluation of the time of onset. The risks and benefits of thrombolysis and the risks and benefits of foregoing treatment should be discussed with the patient, family, or both.

If the patient meets all of the inclusion criteria and none of the exclusion criteria, then the drug should be mixed and administered. Mixing takes 5 to 10 minutes; thus, if time is short, the drug should be prepared in advance. If it

ultimately is not used, it can be returned to the manufacturer for a refund. The dose of tPA is 0.9 mg/kg, 90 mg maximum, 10% given as a bolus over 1 minute, and the remainder infused over 1 hour.

Once the patient has been treated, careful monitoring is required to observe for signs of ICH. Some centers have developed acute stroke units that have been shown to decrease long-term morbidity and mortality compared with standard medical unit care.⁶⁷ If the patient is at an institution that cannot provide the level of care required after treatment, the patient should be transferred as soon as possible to an appropriate facility.⁶⁸ Treatment should not be withheld for transfer as chances for full recovery decline even within the 3-hour window.

Close observation is required for at least the first 24 hours to watch for any signs of an ICH and provide timely interventions. Blood pressure should be strictly monitored and treated if it increases above 180 mm Hg systolic or 105 mm Hg diastolic. Treatment is aimed at lowering the blood pressure to limit the risk of ICH without causing hypotension and extension of the infarction. Drugs such as nifedipine, which can cause precipitous decreases in blood pressure, should be avoided in favor of drugs that can be titrated and have a little effect on CBF, such as labetalol. Antiplatelet or antithrombotic drugs should not be used in the first 24 hours after tPA infusion.

In the NINDS study, early deterioration was observed in 17% of the tPA-treated patients and in 18% of the placebo-treated patients. The most common cause of deterioration in the tPA patients was ICH, whereas complications from untreated stroke (ie, edema) were the cause in the placebo group. The most common signs and symptoms associated with an ICH are decreased level of consciousness, increased weakness, new headache, or sudden increase in blood pressure or pulse. Analyses of posttreatment variables associated with an increased risk of ICH include minor external oozing (at intravenous sites or around the gums; OR 2.3, 95% CI 1.2 to 4.6) and a pulse pressure greater than 50 mm Hg (OR 1.02, 95% CI 1.004 to 1.035). The pulse pressure is highly correlated to mean arterial pressure and the systolic pressure and is an indicator that increased blood pressure after tPA treatment increases the risk of ICH.²¹

If an ICH is suspected in a patient, any remaining infusion of tPA should be stopped, and an immediate CT scan of the brain should be obtained (Table 6). If the scan does not demonstrate an ICH, the tPA infusion may be resumed. Otherwise, blood samples should be sent for coagulation studies and blood products should be prepared. tPA causes a decrease in fibrinogen levels in approximately

30% of patients that can be replaced by cryoprecipitate administration. Neurosurgical consultation should be obtained within 2 hours.⁶⁹ In the NINDS trial, only 1 patient required neurosurgical intervention among 22 who had ICH.²¹ Most institutions already have arrangements for neurosurgical consultations as they receive and care for patients who present with other neurosurgical emergencies such as subarachnoid hemorrhage, traumatic brain injuries, and spontaneous ICH. These same arrangements generally suffice to support thrombolysis in acute ischemic stroke. After the first 24 hours, the standard stroke therapies and workups should proceed as with any other stroke patient.

Managing acute stroke patients in the already busy ED environment requires forethought and planning. Preplanned pathways or protocols allow for rapid and efficient response to pathophysiologic states that require immediate attention and intervention. This is currently done for other disease processes such as trauma, myocardial infarction, and other critical illnesses. The 1996 NINDS consensus conference⁶⁹ established goals for the care of the acute stroke patient in the United States in a manner similar to the National Heart Attack Alert Program. The development of care paths for stroke patients in the ED was specifically recommended. Other goals for emergency care were endorsed: 10 minutes for door to physician time, 25 minutes for door to CT scan, 45 minutes from door to CT scan reading, and 60 minutes for door to drug time. Neurologic expertise should be available within 15 minutes and neurosurgical expertise should be available within 2 hours of patient arrival.

Table 6.

Algorithm for management of intracranial hemorrhage.

1. Monitor neurologic function for signs of deterioration: headache, acute hypertension, nausea, or vomiting.
2. Discontinue tPA if deterioration occurs.
3. Obtain immediate CT scan.
4. Obtain blood samples for prothrombin time, partial thromboplastin time, platelet count, fibrinogen levels.
5. Prepare cryoprecipitate and fibrinogen (6–8 units).
6. Prepare platelets (6–8 units).
7. If ICH is present on CT scan, evaluate laboratory results and consider replacement of fibrinogen.
8. Obtain neurosurgical consultation.
9. Consider consultation with hematologist.
10. Consider repeating CT scan for assessment of progression.
11. Develop consensus for treatment.

As each hospital environment is unique, no single formula is applicable to all, although the tasks are the same.⁷⁰ Flowcharting is a very useful tool that allows a detailed understanding of the current environment and highlights the changes that should be implemented.⁷¹ Fortunately, most of the components are already present and reorganization is all that is required.

CLINICAL EXPERIENCE

Clinical experience (phase 4 studies or postmarketing surveillance data) in treating acute stroke patients provides insight into the feasibility, safety, and efficacy of applying this therapy to daily practice.

The Standard Treatment with Alteplase to Reverse Stroke (STARS) study is the largest prospective report of consecutively treated patients.⁷² STARS reported 3.3% of 389 patients had a symptomatic ICH, with 35% having minimal or no disability, and 43% being independent at 30 days. Together with 7 other published phase 4 studies,⁷³⁻⁷⁹ 940 treated patients had a symptomatic ICH rate of 5.5% and 40% to 44% had a favorable outcome. Tanne et al⁸⁰ also reviewed patients older than 80 years treated in routine clinical practice and found comparable rates of favorable outcome without any increased risk of ICH.

These data compare favorably with the NINDS experience. The lower rate of symptomatic ICH may be explained by fewer patients being treated who have major signs of ischemia on initial CT scan or have a baseline NIH-SSS higher than 20. It appears that patients treated out-of-protocol in clinical practice have a much higher rate of ICH because of significant deviations from established guidelines. Symptomatic ICH rates of 11% to 16% have been reported in studies without prospective protocols in place or among out-of-protocol-treated patients.^{73,75} Treating patients who do not meet the inclusion and exclusion criteria cannot be supported.

FUTURE CHALLENGES

Despite recent advances, most stroke patients do not currently meet treatment inclusion criteria, mainly because of time of presentation. This provides 2 main arenas for future work regarding acute thrombolytic treatment of stroke. One is to find ways to better educate the public about the signs and symptoms of stroke and the need for rapid access to health care using the 911 system. Previous studies have shown that public education can have a dramatic effect on decreasing the time from symptom onset to hospital arrival. In addition, every hospital should

develop protocols for either acute treatment for ischemic stroke or immediate transfer to a facility capable of treatment.⁶⁸ Second, there is a need to continue to find ways to make thrombolytic therapy for stroke safer. This may be done through better patient selection, improvements in patient management (ie, blood pressure), or treatment with other agents that may decrease the risk of hemorrhage.

Beyond thrombolytic treatment within 3 hours, the challenge is to find better methods of reperfusion and adjunctive agents that may either lengthen the therapeutic window or improve clinical efficacy within the therapeutic window.⁸¹ Intra-arterial treatment with pro-urokinase seems promising at this point for patients later than 3 hours after symptom onset. Other interventional techniques are also being studied.⁸² Although most trials with neuroprotective agents to this point have been unsatisfactory, there may be the potential for neuroprotective agents to have beneficial effects when used in combination with reperfusion techniques.⁸³ It is hoped that the addition of neuroprotective agents to reperfusion techniques will both improve clinical efficacy and potentially prolong the therapeutic window, thereby improving the outcome for victims of acute ischemic stroke.

REFERENCES

- American Heart Association. 2000 Heart and Stroke Statistical Update. Dallas, TX: American Heart Association; 1999:13-14.
- Adams HP. Treating ischemic stroke as an emergency. *Arch Neurol.* 1998;55:457-461.
- Major ongoing stroke trials. *Stroke.* 2000;31:557-562.
- Jones TH, Morawetz RB, Crowell RM, et al. Thresholds of focal ischemia in awake monkeys. *J Neurosurg.* 1981;54:773-782.
- Pulsinelli WA. The ischemic penumbra in stroke. *Sci Med.* 1995;1:16-25.
- Hakim AM. Ischemic penumbra, the therapeutic window. *Neurology.* 1998;51(Suppl 3):S44-S46.
- Astrup J, Seisjo BK, Symon L. Thresholds in cerebral ischemia—the ischemic penumbra. *Stroke.* 1981;12:723-725.
- Zivin JA, Choi DW. Stroke therapy. *Sci Am.* 1991;265:56-63.
- DeGraba TJ. The role of inflammation after acute stroke, utility of pursuing anti-adhesion molecule therapy. *Neurology.* 1998;(Suppl 3):S62-S68.
- Choi DW. Ischemia-induced neural apoptosis. *Curr Opin Neurobiol.* 1996;6:667-672.
- The Multicenter Acute Stroke Trial-Europe Study Group. Thrombolytic therapy with streptokinase in acute ischemic stroke. *N Engl J Med.* 1996;335:145-150.
- Multicenter Acute Stroke Trial-Italy (MAST-I) Group. Randomized controlled trial of streptokinase aspirin and combination of both in treatment of acute ischemic stroke. *Lancet.* 1995;346:1509-1514.
- Donnan GA, Davis SM, Chambers BR, et al. For the Australian Streptokinase (ASK) Trial Study Group. Streptokinase for acute ischemic stroke with relationship to time of administration. *JAMA.* 1996;276:961-966.
- Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European cooperative acute stroke study (ECASS). *JAMA.* 1995;274:1017-1025.
- National Institute of Neurologic Disorders in Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med.* 1995;333:1581-1587.

16. Hacke W, Kaste M, Fieschi C, et al. Randomized double blind placebo control trial of thrombolytic therapy with intravenous alteplase in acute ischemic stroke (ECASS-2). *Lancet*. 1998;352:1245-1251.
17. Clark WM, Wissman S, Albers GW, et al. Recombinant tissue plasminogen activator (alteplase) for ischemic stroke 3 to 5 hours after symptom onset, The ATLANTIS Study: a randomized controlled trial. *JAMA*. 1999;282:2019-2026.
18. Shermann DG, Atkinson RP, Chippendale T, et al. Intravenous Ancrod for treatment of acute ischemic stroke The STAT Study: a randomized controlled trial. *JAMA*. 2000;283:2395-2403.
19. International Stroke Trial Collaborative Group. The international stroke trial (IST): a randomized trial of aspirin, subcutaneous heparin, both, or neither among 19,435 patients with acute ischemic stroke. *Lancet*. 1997;349:1569-1581.
20. CAST (Chinese Acute Stroke Trial) Collaborative Group. CAST: randomized placebo-controlled trial of early aspirin use in 20,000 patients with acute ischemic stroke. *Lancet*. 1997;349:1641-1649.
21. The NINDS t-PA Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. *Stroke*. 1997;28:2109-2118.
22. The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. Low molecular weight heparinoid, ORG 10172 (Danaparoid), and outcome after acute ischemic stroke. A Randomized Controlled Trial. *JAMA*. 1998;279:1265-1272.
23. del Zoppo GJ. Clinical trials in acute stroke. Why have they not been successful? *Neurology*. 1998;51(Suppl 3):S59-S61.
24. del Zoppo GJ, Higashida RT, Furlan AJ, et al. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. *Stroke*. 1998;29:4-11.
25. Ferland AJ, Higashida R, Wechsler L, et al. Intra-arterial Prourokinase for acute ischemic stroke. The PROACT II Study: a randomized controlled trial. *JAMA*. 1999;282:2003-2011.
26. TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. *N Engl J Med*. 1985;312:932-936.
27. Egan R, Clark W, Lutsep H, et al. Efficacy of intra-arterial thrombolysis of basilar artery stroke. *J Stroke Cerebrovasc Dis*. 1999;8:22-27.
28. Ferbert A, Bruckman H, Drummen R. Clinical features of proven basilar occlusion. *Stroke*. 1990;21:1135-1142.
29. Hacke W, Zeumer H, Ferbert A, et al. Intra-arterial thrombolytic therapy improves outcome in patients with acute vertebralbasilar occlusive disease. *Stroke*. 1988;19:1216-1222.
30. Lewandowski CA, Frankel M, Tomsick TA, et al. Combined intravenous and intra-arterial r-tPA versus intra-arterial therapy of acute ischemic stroke: Emergency Management of Stroke (EMS) Bridging Trial. *Stroke*. 1999;30:2598-2605.
31. Lewandowski CA, Libman R. Acute presentation of stroke. *J Stroke Cerebrovasc Dis*. 1999;8:117-126.
32. Brott T, Adams HP, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*. 1989;20:864-870.
33. Goldstein LB, Bertels C, Davis JN. Interrater reliability of the NIH stroke scale. *Arch Neurol*. 1989;46:660-662.
34. Adams HP Jr, Brott TG, Crowell RM, et al. Guidelines for the management of patients with acute ischemic stroke. A statement for healthcare professionals from a special writing group of the stroke council, American Heart Association. *Stroke*. 1994;25:1901-1914.
35. Culbras A, Kase CS, Masdeu JC, et al. Practice guidelines for the use of imaging and transient ischemic attacks in acute stroke. Report of the Stroke Council, American Heart Association. *Stroke*. 1997;28:1480-1497.
36. Mohr JP, Biller J, Alou SK, et al. Magnetic resonance versus computed tomographic imaging in acute stroke. *Stroke*. 1995;26:807-812.
37. von Kummer R, Meyding-Lamade U, Forsting M, et al. Sensitivity and prognostic value of early CT in occlusion of the middle cerebral artery trunk. *AJNR Am J Neuroradiol*. 1994;15:9-15.
38. Marks MP, Holmgren EB, Fox AJ, et al. Evaluation of early computed tomographic findings in acute ischemic stroke. *Stroke*. 1999;30:389-392.
39. von Kummer R, Webber J. Brain and vascular imaging in acute ischemic stroke: the potential of computed tomography. *Neurology*. 1997;49(Suppl 4):s52-s55.
40. Tomsick T, Brott T, Barson W, et al. Prognostic value of the hyperdense middle cerebral artery sign and stroke scale score before ultra early thrombolytic therapy. *AJNR Am J Neuroradiol*. 1996;17:79-85.
41. Wildermuth S, Knauth M, Brandt T, et al. Role of CT angiography in patient selection for thrombolytic therapy in acute hemispheric stroke. *Stroke*. 1998;29:935-938.
42. Koenig M, Klotz E, Luka B, et al. Perfusion CT of the brain diagnostic approach for early detection of ischemic stroke. *Radiology*. 1998;209:85-93.
43. Na DG, Buyun HS, Lee KH, et al. Acute occlusion of the middle cerebral artery: early evaluation of tri-phase echolocation CT, preliminary results. *Radiology*. 1998;207:113-122.
44. Firlik AD, Kaufmann AM, Wechsler LR, Firlik KS, Fukui MB, Yonas H. Quantitative cerebral bloodflow determinations in acute ischemic stroke relationship to computed tomography and angiography. *Stroke*. 1997;28:2208-2213.
45. Fisher M, Prichard JW, Warach S. New magnetic resonance techniques for acute ischemic stroke. *JAMA*. 1995;274:908-911.
46. Albers GW. Diffusion weighted MRI for evaluation of acute stroke. *Neurology*. 1998;51(Suppl 3):s47-s49.
47. Fisher M, Albers GW. Applications of diffusion perfusion magnetic resonance imaging in acute ischemic stroke. *Neurology*. 1999;52:1750-1756.
48. Powers WJ. Acute hypertension after stroke: the scientific basis for treatment decisions. *Neurology*. 1993;43:461-467.
49. Broderick J, Brott T, Barsan W, et al. Blood pressure during the first minutes of focal cerebral ischemia. *Ann Emerg Med*. 1993;22:1438-1443.
50. Adams HP, Brott TG, Furlan AJ, et al. Guidelines for thrombolytic therapy for acute stroke: a supplement to the guidelines for the management of patients with acute ischemic stroke. *Circulation*. 1996;94:1167-1174.
51. McDowell FH, Brott TG, Goldstein M, et al. Stroke: the first hours, emergency evaluation, and treatment. National Stroke Association Consensus Statement. *Stroke Clinical Update* (Special edition). 1997;1-14.
52. Lisk DR, Grotta JC, Lamki LM, et al. Should hypertension be treated after acute stroke? A randomized controlled trial using single photon emission computed tomography. *Arch Neurol*. 1993;50:855-862.
53. Dimant J, Grob D. Electrocardiographic changes and myocardial damage in patients with acute cerebrovascular accidents. *Stroke*. 1977;8:448-455.
54. The Hemodilution in Stroke Study Group. Hypervolemic hemodilution treatment of acute stroke. *Stroke*. 1989;20:317-323.
55. Wass CT, Lanier WL. Glucose modulation of ischemic brain injury: review and clinical recommendations. *Mayo Clin Proc*. 1996;71:801-812.
56. Bruno A, Biller J, Adams HP Jr, et al. Acute blood glucose level and outcome from ischemic stroke. *Neurology*. 1999;52:280-284.
57. Reith J, Jorgensen HS, Pedersen PM, et al. Body temperature in acute stroke: relation to stroke severity, infarct size, mortality, and outcome. *Lancet*. 1996;347:422-425.
58. Schwab S, Spranger M, Aschoff A, et al. Brain temperature monitoring and modulation in patients with severe MCA infarction. *Neurology*. 1997;48:762-767.
59. Reith J, Jorgensen HS, Nakayama H, et al. Seizures in acute stroke: predictors and prognostic significance. The Copenhagen Stroke Study. *Stroke*. 1997;28:1585-1589.
60. The NINDS t-PA Study Group. Generalized efficacy of t-PA for acute stroke. Subgroup analysis of the NINDS t-PA stroke trial. *Stroke*. 1997;28:2119-2125.
61. Haley EC, Lewandowski C, Tilley BC, et al. Myths regarding the NINDS rt-PA Stroke Trial: setting the record straight. *Ann Emerg Med*. 1997;30:676-682.
62. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med*. 1991;325:445-453.
63. Albers GW. Atrial fibrillation and stroke. Three new studies, three remaining questions. *Arch Intern Med*. 1994;154:1443-1448.
64. Fagan SC, Morgenstern LB, Pettita A, et al. Cost effectiveness of tissue plasminogen activator for ischemic stroke. *Neurology*. 1998;50:882-900.

-
65. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Practice advisory: thrombolytic therapy for acute ischemic stroke—summary statement. *Neurology*. 1996;47:835-839.
66. Wester P, Radgerg J, Lundgren B, et al. Factors associated with delayed admission to hospital and in-hospital delays in acute stroke and TIA. A prospective, multicenter trial. *Stroke*. 1999;30:40-48.
67. Stroke Unit Trialists' Collaboration. Collaborative systematic review of the randomized trials of organized inpatient (stroke unit) care after stroke. *BMJ*. 1997;314:1151-1159.
68. Alberts M, Hademenos G, Latchaw RE, et al. Recommendations for the establishment of primary stroke centers. *JAMA*. 2000;283:3102-3109.
69. Marler JR, Winters-Jones P, Emr M, eds. National Institute of Neurological Disorders and Stroke, Proceedings of a National Symposium on Rapid Identification and Treatment of Acute Stroke [NIH publication No. 97-4239]. Bethesda, MD: National Institutes of Health; 1997:157-158.
70. The NINDS rt-PA Stroke Study Group. A systems approach to immediate evaluation and management of hyperacute stroke: experience at 8 centers and implications for community practice and patient care. *Stroke*. 1997;28:1530-1540.
71. Tilley BC, Lyden PD, Brott TG, et al. Total quality improvement methodology reduces delays between emergency department admission and treatment of acute ischemic stroke. *Arch Neurol*. 1997;54:1466-1474.
72. Albers GW, the STARS Investigators. Prospective, monitored, multicenter, post-approval experience with intravenous t-PA for treatment of acute stroke: the standard treatment with activase to reverse stroke (STARS) study [abstract]. *Stroke*. 1999;30:244.
73. Katzan IL, Furlan AJ, Lloyd LE, et al. Use of tissue-type plasminogen activator for acute ischemic stroke. The Cleveland experience. *JAMA*. 2000;283:1151-1158.
74. Grund M, Stenzel C, Schmulling S, et al. Early intravenous thrombolysis for acute ischemic stroke in a community-based approach. *Stroke*. 1998;29:1544-1549.
75. Tanne D, Bates VE, Verro P, et al. Initial clinical experience with IV tissue plasminogen activator for acute ischemic stroke: a multicenter survey. The t-PA Stroke Survey Group. *Neurology*. 1999;53:424-427.
76. Smith RW, Scott PA, Grant RJ, et al. Emergency physician treatment of acute stroke with recombinant tissue plasminogen activator: a retrospective analysis. *Acad Emerg Med*. 1999;6:618-625.
77. Chiu D, Krieger D, Villar-Cordova C, et al. Intravenous tissue plasminogen activator for acute ischemic stroke. Feasibility, safety, and efficacy in the first year of clinical practice. *Stroke*. 1998;29:18-22.
78. Buchan AM, Barber PA, Newcommon N, et al. Effectiveness of t-PA in acute ischemic stroke: outcome relates to appropriateness. *Neurology*. 2000;54:679-684.
79. Wang DZ, Rose JA, Honings DS, et al. Treating acute stroke patients with intravenous tPA. The OSF stroke network experience. *Stroke*. 2000;31:77-81.
80. Tanne D, Gorman MJ, Bates VE, et al. Intravenous tissue plasminogen activator for acute ischemic stroke in patients aged 80 years and older: the tPA stroke survey experience. *Stroke*. 2000;31:370-375.
81. del Zoppo GJ, Wagner S, Tagaya M. Trends and future developments in the pharmacologic treatment of acute ischemic stroke. *Drugs*. 1997;54:9-38.
82. Nakano S, Yokogami K, Ohata H, et al. Direct percutaneous transluminal angioplasty for acute middle cerebral artery occlusion. *AJNR Am J Neuroradiol*. 1998;19:767-772.
83. Baird AE, Warach S. Using pathophysiology in acute stroke trials [editorial]. *Stroke*. 1999;30:1293.