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CONTINUUM

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ACUTE ISCHEMIC STROKE

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CONTINUUM
LIFELONG LEARNING IN NEUROLOGY®

EDITOR'S PREFACE

Stroke has long been part of the "bread and butter" of practicing neurologists. For years, the management of acute ischemic stroke, which accounts for an overwhelming majority of cerebrovascular cases, has been a source of frustration and dismay for patients, families, and physicians alike, as effective treatment to reverse a neurologic deficit was lacking. Now, however, despite the availability of thrombolytic therapy that can potentially lead to recovery or at least significant improvement, the exasperation continues as the percentage of patients receiving such treatment languishes in the single digits. The battlegrounds in the struggle to provide better care for the patient with ischemic stroke now include patient education, logistic organization both before and during hospitalization, economic and legal issues, as well as the continuing quest for more effective therapies. A touchstone for the improvement of stroke therapy lies with the education of physicians involved in the treatment of these patients. Indeed, if neurologists wish to retain acute stroke care as part of their "turf," they must be knowledgeable about current best treatment and make themselves available to provide it. In this issue of CONTINUUM, Dr Steven Levine has assembled his own "stroke team," whose members have worked together throughout this issue to promote your understanding of modern acute ischemic stroke care.

A key to more effective stroke management is its prompt recognition. Accurate, as well as rapid, diagnosis is essential. In the first chapter, Drs Kevin Barrett, Joshua Levine, and Karen Johnston review this critical matter, emphasizing not only the importance of distinguishing ischemic from hemorrhagic stroke, but also the exclusion of a variety of conditions that can mimic ischemic stroke. Clearer understanding of the principles of treating stroke is enhanced in the next chapter in which Drs Tudor Jovin, Andrew Demchuk, and Rishi Gupta provide a lucid discussion of the pathophysiology of acute ischemic stroke. Recognition of the importance of the so-called *ischemic penumbra* should drive home the message that for many stroke patients salvation of critical brain tissues is possible.

With these fundamentals under your belt, you will be better equipped to tackle the next three chapters, which address treatment directly, focusing primarily on thrombolytic therapy. First, Drs Pooja Khatri, Joshua Levine, and Jovin address "Intravenous Thrombolytic Therapy for Acute Ischemic Stroke," and then Dr Barrett teams with Drs Khatri and Jovin to examine the very important subject of the prevention and management of the complications of acute ischemic stroke and its treatment. *Time is brain* has become an appropriate mantra for the delivery of better acute stroke care, and the earlier chapters have emphasized its importance. Yet, no matter what we do, many

patients will fail to reach the hospital within the short timeframe currently recommended for administration of IV thrombolytic therapy. In the next chapter, Drs Demchuk, Gupta, and Khatri combine to discuss emerging therapies not only for hyperacute patients, but also for those whose treatment must be delayed beyond 6 hours.

Contemporary effective stroke care is complex, and its optimization requires the cooperation and efforts of many individuals with different training and skills. Regulatory agencies, including the federal and local governments, have gotten into the act; and reimbursement conditions make it attractive for a hospital to be able to deliver topnotch stroke treatment. In the next chapter, Drs Steven Levine, David Adamowicz, and Johnston address many issues under the rubric of "Primary Stroke Center Certification." In order for the development of more effective stroke therapy, much clinical research remains to be done. This will best be accomplished through the participation not only of "academic" neurologists, but also of those working in the trenches as "community" neurologists. In the final didactic chapter of this issue, Drs Steven Levine, Adamowicz, and Johnston partner in providing a "'How To' Guide for Clinicians Interested in Becoming Involved in Clinical Stroke Research."

The physician dealing with stroke patients is often confronted with knotty ethical dilemmas. Drs O. O. Zaidat, Junaid Kalia, and John R. Lynch discuss the care of a patient with locked-in-syndrome in the Ethical Perspectives in Neurology section. Although this is a very unusual outcome of stroke, the principles discussed are generalizable. In this issue, we also reintroduce a section on Practice Issues in Neurology, and I am very pleased that Dr Larry Goldstein, himself a well-recognized stroke specialist at Duke University, has agreed to serve as CONTINUUM's Associate Editor for Practice. Drs Lawrence Wechsler and Syed Zaidi discuss some issues related to consent for thrombolytic therapy.

As usual, a series of exercises that follow the didactic portions of CONTINUUM will help you fortify your knowledge of acute ischemic stroke and recognize those areas in which you might still need to "bone up." Drs Ronnie Bergen and Eduardo Benarroch will challenge you with their multiple-choice questions, and Drs Gupta and Joshua Levine will help you apply the information on current therapy as you work through the patient management problem.

Accompanying this issue is another edition of Quintessentials. If you have not yet tried the new streamlined version of QE—or even if you have—I invite you to engage in this highly clinical exercise that will help you test your knowledge of the subject of acute ischemic stroke management. You will work through a couple of case vignettes, and then a month later you will have the opportunity to repeat the process with new, but similar, cases to see whether you have acquired and maintained the recommended management principles.

Many of our subscribers may not yet have realized that you now have the option to access CONTINUUM online. Now would be a great time to try this service, which has several recent enhancements. Not only can you access the full text of CONTINUUM, but you can answer the multiple-choice questions and receive instant feedback as well as CME credits within two business days. In addition, you can now perform a keyword search of CONTINUUM, access and download key points for each chapter and for each issue as whole, and obtain PowerPoint slides of the figures and tables for your own use as teaching tools. The AAN and the CONTINUUM staff are very pleased to offer these improvements to our online capabilities and welcome your feedback and suggestions.

I am grateful to Dr Steven Levine for using the team approach to which he is accustomed as a provider of stroke care to build a collaborative group of experts who have provided an outstanding CONTINUUM issue. I am confident that utilization of the didactic material, as well as the many other educational opportunities provided, will enable you to deliver the best stroke care possible and help to reduce the huge number of severely affected patients that currently makes this condition the leading cause of long-term disability in the United States.

— Aaron E. Miller, MD

DIAGNOSIS OF STROKE AND STROKE MIMICS IN THE EMERGENCY SETTING

Kevin M. Barrett, Joshua M. Levine, Karen C. Johnston

ABSTRACT

Patients with suspected stroke require urgent evaluation in order to identify those who may be eligible for time-sensitive therapies. A focused and systematic approach to diagnosis improves the likelihood of identifying patients with probable ischemic stroke and minimizes the chances of exposing patients with alternate diagnoses to potentially harmful treatment. This chapter emphasizes the historical, examination, and neuroimaging findings useful in the rapid evaluation and diagnosis of patients with suspected ischemic stroke. Other entities that may present with strokelike symptoms will also be discussed.

Continuum Lifelong Learning Neurol 2008;14(6):13–27.

Note: Text referenced in the Quintessentials Preferred Responses, which appear later in this issue, is indicated in yellow shading throughout this chapter.

KEY POINT

- The ability to treat acute ischemic stroke patients with IV thrombolysis or endovascular therapies depends on accurately establishing the time of symptom onset.

INTRODUCTION

Stroke typically presents with the sudden onset of focal neurologic deficits. Appropriate delivery of acute stroke therapies depends on accurately establishing the time of symptom onset, performing a focused bedside assessment, and rapidly interpreting ancillary tests. This chapter emphasizes a systematic diagnostic approach that will facilitate expeditious identification of patients eligible for acute therapies. By necessity, the discussion that follows is presented sequentially. However, it is important to recognize that many elements of the stroke evaluation occur in parallel, depending on resource availability or clinical circumstances. Specific evidence-based stroke therapies are covered in a subsequent chapter.

BEDSIDE ASSESSMENT

History

The ability to treat acute ischemic stroke patients with IV thrombolysis or endovascular therapies depends on accurately establishing the time of symptom onset. Under ideal circumstances, the patient is able to provide a

Relationship Disclosure: Drs Barrett and Levine have nothing to disclose. Dr Johnston has received personal compensation for activities with AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Inc., Diffusion Pharmaceuticals LLC, NIH–National Institute of Neurological Disorders and Stroke, Ono Pharmaceutical Co., Ltd, Remedy Pharmaceuticals, and sanofi-aventis. Dr Johnston has received personal compensation in an editorial capacity from *Up-to-Date* and *Neurology*.
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detailed account of symptom onset. The history should focus on eliciting information that will establish eligibility for thrombolytic therapy or identify potential exclusionary conditions. Situations may arise in which the precise time of symptom onset may be difficult to establish. The use of cues (eg, ''before or after lunch?'' or ''before or after the evening news?'') may be helpful in generating an estimated time of onset. If family or friends are present, it is wise to corroborate the patient's report of symptom onset with eyewitnesses. In some circumstances, a precise time of symptom onset will prove impossible to determine, and the line of questioning should then shift to identifying when the patient was last neurologically normal. For those patients who awaken with symptoms, the time of onset becomes the time at which they went to bed (assuming they were normal at that time). For patients with heralding symptoms or TIA, it is necessary to ensure complete resolution before the clock can be ''reset.''

The nature of symptom onset should be obtained when possible. Symptoms that begin abruptly suggest a vascular etiology, whereas symptoms that begin in one region and gradually spread to involve other areas may support an alternate etiology (ie, migraine). Inquiry should be made regarding risk factors for vascular disease, as well as any history of seizures, migraine, insulin use, or drug abuse that may support another cause for the patient's symptoms. Information necessary for decisions regarding thrombolysis must be obtained in a structured fashion to minimize the possibility of overlooking critical information (**Table 1-1**). Accompanying symptoms, particularly headache, warrant further exploration. Ictal, or so-called thunderclap headache, should alert the clinician to the possibility of subarachnoid hemorrhage. Small bleeds or sentinel leaks from unruptured intracranial aneurysms may not be evident on CT scan. Further evaluation with lumbar puncture to exclude the presence of blood in the subarachnoid space may be warranted (Edlow and Caplan, 2000).

TABLE 1-1 Important Historical Information in the Suspected Stroke Patient

▶ **History of the Present Illness**
Time of symptom onset
Evolution of symptoms
Convulsion or loss of consciousness at onset
Headache
Chest pain at onset
▶ **Medical History**
Prior intracerebral hemorrhage
Recent stroke
Recent head trauma or loss of consciousness
Recent myocardial infarction
▶ **Surgical History**
Recent surgical procedures
Arterial puncture
▶ **Review of Systems**
Gastrointestinal or genitourinary bleeding
▶ **Medications**
Anticoagulant therapy

The initial evaluation of the potential stroke patient often occurs in a high-acuity area. Medical personnel responsible for establishing IV access, initiating cardiorespiratory monitoring, performing blood draws, and performing electrocardiography compete for the patient's attention. Additionally, the presence of aphasia or neglect may limit the patient's ability to provide accurate

information. To the physician performing the initial assessment, these activities pose significant challenges.

Despite such barriers, critical elements of the history may be obtained indirectly. Emergency medical personnel provide important information regarding vital signs and blood glucose levels obtained in the field. Observations regarding level of consciousness, initial severity of deficits, and the presence of bowel or bladder incontinence at the scene provide useful clues to the etiology of the presenting symptoms. Family members provide important observations and additional history. Reaching a family member by telephone may be necessary if no one is immediately available. In certain circumstances, attempting to reach the patient's primary care provider may prove useful. Documentation of prior stroke, TIA, or other neurologic morbidity in medical records is valuable. Chronic or previously resolved deficits may potentially confound interpretation of neurologic examination findings in the acute setting. The presence of advanced dementia or other neurodegenerative process may influence the decision to pursue further aggressive interventions. Examination of medication bottles, if they accompany the patient, may provide clues to coexisting medical conditions or anticoagulant use.

Neurologic Examination

The examination should focus on identifying signs of lateralized hemispheric or brainstem dysfunction consistent with focal cerebral ischemia. Commonly encountered ischemic stroke syndromes are outlined in **Table 1-2**. The location of vascular occlusion and

KEY POINT

- The examination should focus on identifying signs of lateralized hemispheric or brainstem dysfunction consistent with focal cerebral ischemia.

TABLE 1-2 Common Ischemic Stroke Syndromes

Vascular Territory	Signs and Symptoms
Left middle cerebral artery distribution	Aphasia, right hemiparesis/hemisensory disturbance, right homonymous hemianopia, left head and gaze preference
Right middle cerebral artery distribution	Left hemispatial neglect, left hemiparesis/hemisensory disturbance, left homonymous hemianopia, right head and gaze preference, anosognosia
Left posterior cerebral artery distribution	Right visual field defect, impaired reading with intact writing (alexia without agraphia), poor color naming, right hemisensory disturbance
Right posterior cerebral artery distribution	Left visual field defect, visual neglect, left hemisensory disturbance
Vertebrobasilar distribution	Dizziness, vertigo, nausea, diplopia, quadriparesis, crossed motor or sensory findings (ipsilateral face, contralateral body), truncal or limb ataxia, visual loss/dimming, impaired consciousness
Penetrating artery distribution (ie, lacunar syndromes)	
(A) Internal capsule/corona radiata (B) Ventral pons	(A, B) Contralateral hemiparesis alone (pure motor stroke) OR contralateral hemiparesis + ataxia out of proportion to weakness (ataxic-hemiparesis); no cortical signs
(C) Thalamus	(C) Contralateral sensory loss alone (pure sensory stroke); no cortical signs

KEY POINTS

- The NIH Stroke Scale is a validated, 15-item scale, which is utilized to assess key components of the standard neurologic examination in patients with stroke.
- Cardiac enzymes and a 12-lead EKG are recommended for all patients with stroke.

the extent of collateral flow dictate whether the complete or partial syndrome is present. Frequently, important examination findings are observed while obtaining the history. Thus, level of consciousness and the presence of a gaze deviation, aphasia, neglect, or hemiparesis, may be established within minutes of the initial encounter. The NIH Stroke Scale (NIHSS) is a validated 15-item scale that is used to assess key components of the standard neurologic examination and measure stroke severity (Lyden et al, 1999). Although initially designed to measure clinical differences in experimental stroke therapy trials (Brott et al, 1989), the NIHSS has gained widespread acceptance as a standard clinical assessment tool. The scale assesses level of consciousness, ocular motility, facial and limb strength, sensory function, coordination, language, speech, and attention. Scores range from 0 (normal) to 42 (maximal score) (**Table 1-3**). The NIHSS may be performed rapidly and predicts short-term and long-term neurologic outcomes (Adams et al, 1999). Even health care providers without expertise in the neurologic examination may be trained to perform the assessment reliably with only a few hours of instruction (Goldstein and Samsa, 1997). Additionally, NIHSS severity may provide information regarding the likelihood of identifying a large vessel occlusion with vascular imaging (Fischer et al, 2005).

The NIHSS has important limitations. It does not include a detailed assessment of the cranial nerves, and relatively low scores may occur in patients with disabling brainstem or cerebellar infarction (Kasner, 2006). Likewise, milder deficits caused by focal cerebral ischemia, such as impaired hand dexterity or fine finger movements, may escape detection if not specifically tested. Stroke severity may not be accurately reflected in nondominant hemisphere syndromes as compared with dominant hemisphere strokes (Woo et al, 1999), and a reliable score is often difficult to obtain in patients with encephalopathy or cognitive dysfunction. Clinically important changes on serial examination may not be reflected as a measurable change on the NIHSS. Finally, one should recognize that the presence of an abnormality on the NIHSS does not support or refute a diagnosis of stroke. As discussed below, many other conditions may cause strokelike symptoms and NIHSS abnormalities.

Findings on general physical examination may facilitate stroke diagnosis and influence treatment decisions. As in any critically ill patient, the first priority is assessment and stabilization of the patient's airway, breathing, and circulation. When performing the general examination, attention should be focused on the cardiovascular system. The presence of a cervical bruit, cardiac murmur, or irregularly irregular heart rhythm may provide an important clue to the underlying stroke mechanism. Unequal extremity pulses may suggest aortic dissection or the presence of concomitant peripheral arterial disease. Funduscopic examination may reveal signs of chronic hypertensive arterial disease or endocarditis. Signs of head or neck trauma (eg, contusions, lacerations) prompt consideration of occult cervical spine injury. Other findings, such as rales on chest examination or bilateral asterixis, may suggest an alternate explanation (ie, pneumonia or metabolic encephalopathy) for the patient's symptoms.

Ancillary Testing

Laboratory and cardiac evaluation supplement the clinical impression derived from the bedside assessment. Some conditions that may present with strokelike symptoms may be identified based on laboratory results (eg,

hypoglycemia). In addition, abnormal laboratory values may exclude patients from receiving thrombolytic therapy. Recently published guidelines recommend routine laboratory testing of blood glucose, electrolytes, complete blood count, prothrombin time, activated partial thromboplastin time, international normalized ratio, and renal function (Adams et al, 2007). Testing for stool guaiac is not routinely recommended unless an indication exists (eg, melena or hematochezia). Initiating treatment with IV recombinant tissue-type plasminogen activator (rt-PA) prior to obtaining results of coagulation studies may be safe and feasible (Sattin et al, 2006). In patients otherwise eligible for thrombolytic therapy, the American Heart Association/American Stroke Association (AHA/ASA) guidelines support the decision to initiate treatment prior to results of platelet or coagulation studies, unless a bleeding disorder or thrombocytopenia is suspected.

Cardiac abnormalities are common in patients with stroke. Cardiac enzymes and a 12-lead EKG are recommended for all stroke patients. Myocardial infarction and atrial fibrillation are common causes of cardioembolism and are readily identified in the acute setting. The utility of routine chest radiography as part of the acute stroke evaluation is limited (Sagar et al, 1996) and currently not routinely recommended. As discussed previously, unless warranted by the presence of sudden, severe headache, there is no role for routine CSF examination. Urine toxicology screen, blood alcohol level, arterial blood gas, or pregnancy tests may be indicated when the clinical history is limited or uncertain.

NEUROIMAGING

Brain imaging is the only reliable means to differentiate between ischemic and

TABLE 1-3 NIH Stroke Scale[a]

Category	Scale Definition
1a. Level of consciousness	0 = Alert 1 = Not alert, arousable 2 = Not alert, obtunded 3 = Unresponsive
1b. Questions	0 = Answers both correctly 1 = Answers one correctly 2 = Answers neither correctly
1c. Commands	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task
2. Gaze	0 = Normal 1 = Partial gaze palsy 2 = Total gaze palsy
3. Visual fields	0 = No visual loss 1 = Partial hemianopsia 2 = Complete hemianopsia 3 = Bilateral hemianopsia
4. Facial palsy	0 = Normal 1 = Minor paralysis 2 = Partial paralysis 3 = Complete paralysis
5a. Left motor arm	0 = No drift 1 = Drift before 10 seconds 2 = Falls before 10 seconds 3 = No effort against gravity 4 = No movement
5b. Right motor arm	0 = No drift 1 = Drift before 10 seconds 2 = Falls before 10 seconds 3 = No effort against gravity 4 = No movement
6a. Left motor leg	0 = No drift 1 = Drift before 5 seconds 2 = Falls before 5 seconds 3 = No effort against gravity 4 = No movement
6b. Right motor leg	0 = No drift 1 = Drift before 5 seconds 2 = Falls before 5 seconds 3 = No effort against gravity 4 = No movement
7. Ataxia	0 = Absent 1 = One limb 2 = Two limbs

continued on next page

TABLE 1-3 *Continued*

Category	Scale Definition
8. Sensory	0 = Normal 1 = Mild loss 2 = Severe loss
9. Language	0 = Normal 1 = Mild aphasia 2 = Severe aphasia 3 = Mute or global aphasia
10. Dysarthria	0 = Normal 1 = Mild 2 = Severe
11. Extinction/inattention	0 = Normal 1 = Mild 2 = Severe

[a]The full NIH Stroke Scale with instructions and scoring sheet is available online at *www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf*. Accessed August 20, 2008.

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Data from National Institute of Neurological Disorders and Stroke. [accessed July 28, 2008] Available at *www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf*. Accessed August 20.

hemorrhagic stroke and is therefore mandatory prior to thrombolytic therapy (Besson et al, 1995; Mader and Mandel, 1998). This chapter will cover the basics of standard CT and MRI used in the emergency setting. More advanced vascular and physiologic imaging will be discussed in another chapter.

CT

Noncontrast head CT is the study most readily available in most stroke centers. CT is sensitive to intracranial blood and may be rapidly performed as part of the acute stroke evaluation. CT is also inexpensive and less susceptible than MRI to artifact introduced by patient movement. In the acute setting, early ischemic change (EIC) may be apparent on CT. Loss of differentiation of the gray-white matter interface, particularly in the region of the insular cortex or the lentiform nucleus, may be indicative of early cerebral ischemia. Sulcal effacement, representing focal tissue edema, may be appreciated in areas of relative hypoperfusion and may be another early indicator of ischemia. Whether these changes are present in the minutes to hours after symptom onset is probably related to the severity and extent of ischemia, collateral circulation, and presence of large vessel occlusion. Detection of EIC is variable (Grotta et al, 1999) and is likely related to reader experience. One study identified EICs in 75% of patients presenting within 3 hours of symptom onset (Barber et al, 2000), and an even higher prevalence was observed within 6 hours in patients with hemispheric strokes (von Kummer et al, 1996). The presence of EICs involving greater than one-third of the middle cerebral artery (MCA) territory was used as an exclusion criterion in early clinical trials of thrombolytics in an effort to minimize the risk of hemorrhagic complications (Hacke et al, 1995). The presence of EICs, however, was not independently associated with adverse outcome after rt-PA treatment in the National Institute of Neurological Disorders and Stroke (NINDS) trial and therefore should not preclude thrombolytic therapy in otherwise eligible patients (Patel et al, 2001).

Increased CT attenuation within an arterial segment, the ''hyperdense'' artery sign, is an occasional finding. It is observed most commonly in the MCA and is associated with occlusive thrombus within the vessel lumen (Tomsick et al, 1989) (**Figure 1-1**). Although the hyperdense MCA sign is fairly specific for vascular occlusion (Bastianello et al, 1991), the sensitivity

of this finding is low. The MCA ''dot sign'' seen in the sylvian fissure with occlusion of distal MCA branches (Barber et al, 2001) and the hyperdense basilar artery sign in patients with basilar artery thrombosis (Ehsan et al, 1994) have also been described. A recent systematic review of studies reporting on early CT signs in acute ischemic stroke found interobserver agreement to be moderate to poor and increased likelihood of poor functional outcome when early infarction signs were present (Wardlaw and Meilke, 2005). An example of early ischemic changes is demonstrated in **Case 1-1**.

The appearance of ischemic changes on CT evolves over time. Within 12 to 24 hours, an indistinct area of low density becomes apparent in the affected vascular distribution. After 24 hours, the ischemic region becomes increasingly hypodense and better circumscribed. Mass effect develops and results in sulcal asymmetry or ventricular distortion. The presence of a clearly delineated area of hypodensity with associated mass effect should, therefore, prompt reassessment of the time of symptom onset in patients thought to be eligible for thrombolytic therapy, as distinct hypodensity is inconsistent with focal cerebral ischemia of less than 3 hours' duration.

Neurologists involved in the evaluation of patients with acute stroke must be sufficiently skilled to identify radiographic contraindications to thrombolytic therapy. Generally speaking, a ''central to peripheral'' approach to visual inspection of CT images may help to rapidly identify nonischemic causes of strokelike symptoms and to identify subtle EIC. First, inspection of the midline structures (ie, ventricles and basal cisterns) for shift may help rapidly identify space-occupying mass lesions, which may require urgent surgical intervention. The basal cisterns,

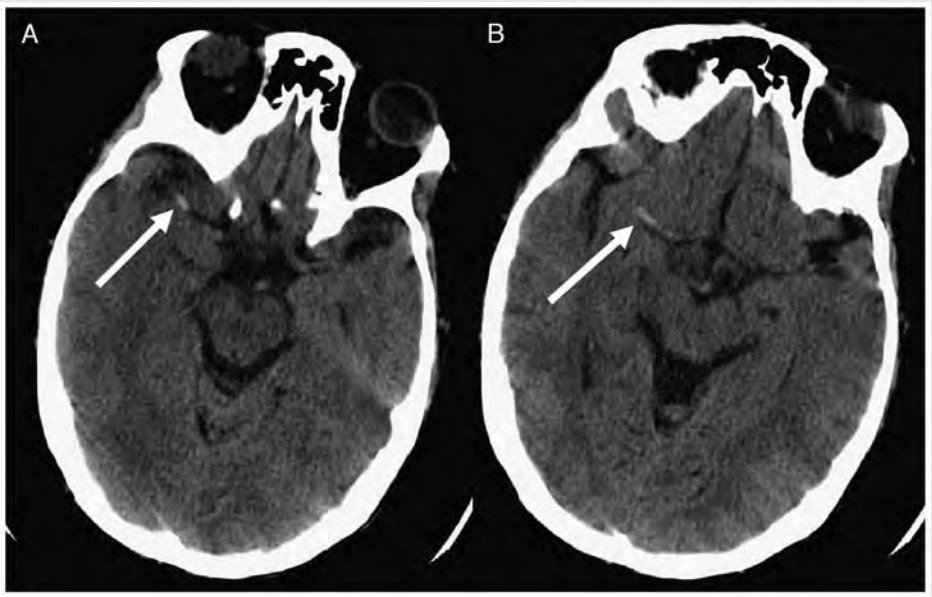

FIGURE 1-1 Noncontrast head CT from a 74-year-old woman with the abrupt onset of dysarthria and left-sided weakness. The hyperdense right middle cerebral artery (*arrows*) is visible on these axial images at two sequential levels (*A, B*). Follow-up cerebral angiography confirmed occlusion of the proximal right middle cerebral artery.

KEY POINTS

- Brain imaging is the only reliable means to differentiate between ischemic and hemorrhagic stroke and is therefore mandatory prior to instituting thrombolytic therapy.
- CT is sensitive to intracranial blood, is widely available, and may be rapidly performed as part of the acute stroke evaluation.
- Loss of differentiation of the gray-white matter interface, particularly in the region of the insular cortex or the lentiform nucleus, may be indicative of early cerebral ischemia.
- Sulcal effacement, representing focal tissue edema, may be appreciated in areas of relative hypoperfusion and may be another early indicator of ischemia.

KEY POINTS

- Increased CT attenuation within an arterial segment, the ''hyperdense'' artery sign, is an occasional finding in acute ischemic stroke.
- The appearance of ischemic changes on CT evolves over time.

Case 1-1

A 48-year-old man was seen by the acute stroke intervention team after he had developed left-sided weakness. He was last known to be normal 2 hours earlier. The patient reported mild headache but otherwise denied any problems.

Neurologic examination demonstrated a right head and gaze preference, left homonymous hemianopsia, left lower facial weakness, dysarthria, and dense left hemiparesis with absent sensation in the left arm and leg. The patient did not acknowledge the presence of his left-sided weakness. His NIHSS score was 14. Noncontrast head CT demonstrated a large area of subtle hypodensity with loss of the gray-white interface in the insular ribbon (*white arrow*) consistent with right MCA distribution ischemia. Sulcal effacement and blurring of the deep nuclei (*arrowhead*) are also seen (**Figure 1-2**).

Comment. This case exemplifies early ischemic changes that may be seen with CT in the early hours after stroke onset. The clinical syndrome fit well with a nondominant hemisphere ischemic event, and the early ischemic changes appreciable on noncontrast CT helped confirm the clinical assessment. The patient underwent emergent vascular imaging and was found to have a right internal carotid artery occlusion.

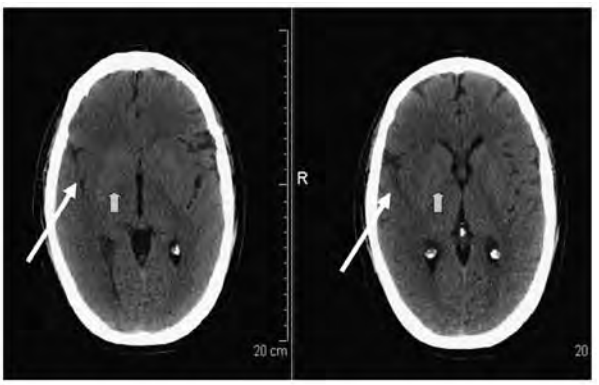

FIGURE 1-2

interhemispheric fissure, and sylvian fissures should be scrutinized for subarachnoid blood. The fourth ventricle should be identified, particularly in patients with posterior circulation symptoms. Although CT evaluation of the posterior fossa may be challenging because of technical limitations, distortion of the fourth ventricle may result from mass effect related to cerebellar infarction and often heralds obstructive hydrocephalus due to evolving edema. Examination of the periphery of the brain parenchyma for extraaxial collections should follow. The brain parenchyma should approximate the inner table of the skull in a fairly symmetric fashion, acknowledging that atrophy may occur in a regional distribution. As with ischemic changes, the appearance of subdural collections evolves with time and these may appear isodense to brain parenchyma. Finally, careful inspection for early ischemic changes (see above) may be guided by localizing information from the clinical examination. Effective and timely administration of acute stroke therapy relies on accurate bedside assessment and exclusion of intracranial

hemorrhage. Subtle changes of early ischemia, while helpful in confirming clinical suspicion, are often identified with the assistance of a radiologist and should not directly influence therapeutic decisions.

MRI

Evaluation of patients with acute stroke with MRI has clear advantages. Compared with CT, MRI with diffusion-weighted imaging (DWI) sequences is more sensitive for acute cerebral ischemia and improves diagnostic accuracy (Fiebach et al, 2002). DWI may detect abnormalities within minutes after onset of cerebral ischemia (Hjort et al, 2005) and delineates the location, size, and extent of hyperacute ischemia. MRI better evaluates the posterior fossa and improves visualization of small cortical infarctions (**Figure 1-3**).

Historical concerns about the ability of MRI to identify acute intracerebral hemorrhage have been addressed by several studies. Conventional T1-weighted and T2-weighted MRI pulse sequences are able to identify subacute and chronic blood, but they are less sensitive for parenchymal hemorrhage during the first 6 hours after symptom onset. Susceptibility-weighted MRI, or gradient-recalled echo (GRE), sequences have improved sensitivity for recently extravasated blood products (Patel et al, 1996). A prospective study of MRI and CT performed within 6 hours of stroke symptom onset demonstrated that the accuracy of GRE sequences for acute hemorrhage is equal to that of CT (Kidwell et al, 2004). A smaller multicenter study found a similarly high accuracy of GRE for identification of acute intracerebral hemorrhage (Fiebach et al, 2004).

Some centers have developed extensive experience with MRI in acute stroke and have adopted the use of MRI protocols for routine evaluation of patients with stroke. A recent prospective study performed at such a center demonstrated the superiority of MRI for detection of acute stroke in the full spectrum of patients who presented for emergency assessment of strokelike symptoms (Chalela et al, 2007). Based on these results, the authors have advocated the use of MRI as the sole modality in the evaluation of patients with suspected stroke. The utility of MRI in detecting subarachnoid hemorrhage has not been rigorously evaluated, and only limited data are available (Wiesmann et al, 2002). The previous studies of MRI for the acute evaluation of stroke were performed using 1.5 tesla (T) magnets. Further studies will be needed to clarify the role of newer generation 3T MRI scanners for hyperacute stroke diagnosis.

KEY POINTS

- Diffusion-weighted imaging is more sensitive for detection of acute cerebral ischemia and improves diagnostic accuracy.
- A prospective study of MRI and CT performed within 6 hours of stroke symptom onset demonstrated that the accuracy of gradient-recalled echo sequences for acute hemorrhage is equal to that of CT.

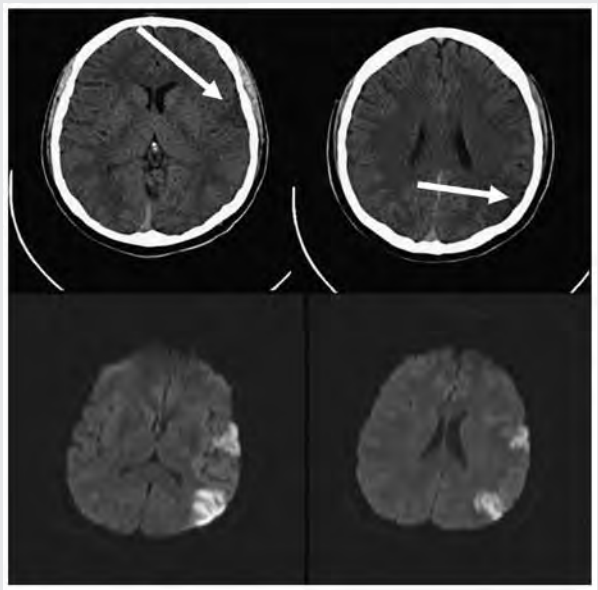

FIGURE 1-3 CT and MRI images from a 39-year-old man who developed sudden speech difficulty. The CT images (*top row*) demonstrate hypodensity in the posteroinferior left frontal (*top left, white arrow*) lobe and adjacent superior left temporal lobe as well as loss of gray-white junction and sulcal effacement in the posterior parietal region (*top right, white arrow*). MR diffusion-weighted images (*bottom row*) demonstrate the abnormalities clearly (*bright signal*).

KEY POINTS

- When acute ischemic stroke is suspected, it is crucial to consider and to exclude alternative diagnoses, especially intracranial hemorrhage.
- Many conditions, including systemic abnormalities and other nervous system diseases, present with focal neurologic deficits that ''mimic'' acute ischemic stroke.
- A recent prospective study of more than 300 patients who presented to an urban teaching hospital with suspected stroke found mimics in 31% at the time of final diagnosis.

The vast majority of emergency departments lack the resources necessary to perform emergent MRI. The costs of the technology, including around-the-clock technician support, are prohibitive for many centers and have limited widespread implementation. Abbreviated stroke MRI protocols have been developed to address concerns about additional time needed to acquire MRI images compared with CT. This issue is important given the association between time to initiation of thrombolytic therapy and likelihood of an excellent neurologic outcome (Marler et al, 2000). MRI is contraindicated in patients with pacemakers or other metallic hardware and is further limited by its susceptibility to motion artifact in agitated patients.

STROKE MIMICS

When acute ischemic stroke is suspected, it is crucial to consider and to exclude alternative diagnoses, especially intracranial hemorrhage. Many conditions, including systemic abnormalities and other nervous system diseases, present with focal neurologic deficits that ''mimic'' acute ischemic stroke. **Table 1-4** lists commonly encountered stroke mimics. Some stroke mimics may be discovered early during the course of evaluation (eg, hypoglycemia), but others may require more extensive investigation and/or neuroimaging (**Case 1-2**). The history and examination help determine the probability of a stroke mimic as the cause of neurologic dysfunction. Distinguishing features of some stroke mimics are highlighted in **Table 1-5**.

Early studies found the frequency of stroke mimics range from 1% (O'Brien et al, 1987) to 19% (Libman et al, 1995) in patients with suspected or initially diagnosed stroke. The time of patient assessment relative to symptom onset, examiner experience, and availability of imaging results at the time of initial diagnosis were variable in these studies. A recent prospective study of more than 300 patients who presented to an urban teaching hospital with suspected stroke found mimics in 31% at the time of final diagnosis (Hand et al, 2006). The most frequent mimics were postictal deficits (21%), sepsis (13%), and toxic-metabolic disturbances (11%). Seventy-five percent of mimics in the study were neurologic disorders, and 42% of patients with a mimic had experienced a previous stroke. Eight variables independently associated with a correct diagnosis were identified. The most powerful predictors of an accurate stroke diagnosis were ''definite history of focal neurologic symptoms'' (odds ratio [OR] 7.21; 95% confidence interval [CI], 2.48–20.93) and an NIHSS score greater than 10 (OR 7.23; 95% CI, 2.18–24.05). In patients with known cognitive impairment, the likelihood of having a stroke was markedly reduced (OR 0.33; 95% CI, 0.14–0.76).

While studies such as these improve our general understanding of the

TABLE 1-4 Common Acute Stroke Mimics

- Postictal deficits (Todd paralysis)
- Hypoglycemia
- Migraine (hemiplegic, with aura)
- Hypertensive encephalopathy
- Reactivation of prior deficits
- Mass lesions
- Subarachnoid hemorrhage
- Peripheral vestibulopathy
- Conversion reaction

Case 1-2

An 82-year-old woman was seen by the acute stroke intervention team for the sudden onset of speech difficulty 90 minutes earlier. She had been working with a physical therapist at home when she became unable to speak. There was no associated weakness, alteration of consciousness, or headache. Per report, she had experienced a minor ''stroke'' approximately 2 weeks earlier but had made some improvement.

The woman was afebrile, her initial blood pressure was 142/72 mm Hg, and the finger-stick glucose level was 188 mg/dL. She was awake, alert, and appropriate. Language examination was remarkable for impaired fluency with the ability to say only fragments of words. She was able to follow simple midline commands but was unable to follow complex commands. She was unable to repeat, read, or name objects. There was no limb weakness or sensory disturbance. Her NIHSS score was 6.

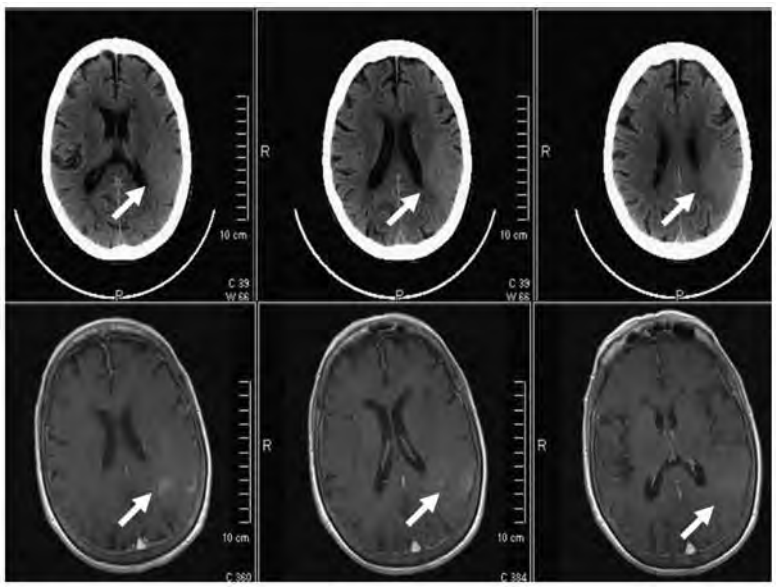

FIGURE 1-4

Noncontrast head CT demonstrated a subtle hyperdense lesion with mass effect involving the left temporoparietal region (**Figure 1-4**, *top, arrows*). Given the radiographic findings suggestive of an underlying structural lesion, the patient did not receive thrombolytic therapy. Follow-up MRI demonstrated an ill-defined enhancing lesion involving the white matter and cortex of the left parietal lobe suggestive of a low-grade neoplasm (**Figure 1-4**, *bottom, arrows*).

Comment. This case is an example of a stroke mimic. The abrupt onset of symptoms might not prompt initial consideration of an underlying structural lesion as a potential etiology. However, one study found that 6% of patients with brain tumors presenting to an emergency department had symptoms of less than 1 day's duration (Snyder et al, 1993). Sudden onset of focal symptoms in patients with either diagnosed or undiagnosed tumors may result from seizures, hemorrhage into the tumor, or obstructive hydrocephalus caused by increasing mass effect.

TABLE 1-5 Characteristics of Common Stroke Mimics

Diagnosis	Comments
Seizure (postictal)	Focal deficits likely are caused by seizure-induced neuronal dysfunction (reversible). May occur with simple partial or generalized seizures. Clinical seizure is often unwitnessed or unrecognized. Spontaneous resolution occurs over hours (may last up to 48 hours).
Hypoglycemia	Aphasia or hemiplegia may be present. Variable drowsiness or obtundation. Blood glucose usually <45 mg/dL. Resolution of symptoms (immediate→hours) with IV glucose.
Metabolic encephalopathy	Etiologies include hyperosmolar hyperglycemia, hyponatremia, and hepatic encephalopathy. May be associated with altered level of consciousness, poor attention, or disorientation (eg, delirium) asterixis.
Conversion reaction	Diagnosis of exclusion. Conversion disorder is the most common psychiatric diagnosis. Comorbid psychiatric problems are common. Paresis, paralysis, and movement disorders are common.
Reactivation of prior deficits	Imaging evidence or history of remote stroke is often apparent. Previous deficit may have resolved completely.

frequency and nature of stroke mimics, the results are less applicable to individual patients. As emphasized previously, the diagnosis of stroke is based on a composite of information obtained from the history and the pattern of findings on physical examination. A single symptom or sign cannot be used to rule in or rule out the diagnosis (Goldstein, 2006).

STROKE CHAMELEONS

The clinician should also be aware of common atypical stroke presentations. Recognition of these entities is important so as not to miss an opportunity to offer treatment to an otherwise eligible patient with stroke. These patients may not be triaged into acute stroke pathways and, therefore, may be at higher risk of misdiagnosis. The term *stroke chameleon* has been aptly used to describe an atypical stroke presentation that appears to mimic another disease process (Huff, 2002). The clinician should suspect such problems when symptom onset is abrupt or occurs in patients with risk factors for cerebrovascular disease.

A small proportion of patients with stroke may present with symptoms suggestive of an acute confusional state (eg, delirium). While encephalopathy typically reflects diffuse hemispheric dysfunction, a ''pseudo-encephalopathy'' may occur with focal cerebral ischemia involving the limbic cortex or orbitofrontal regions. ''Confusion'' may also be reported in patients with fluent aphasia or neglect syndromes without accompanying motor deficits. Systematic neurologic examination should identify these focal features and increase the clinical suspicion of stroke. Likewise, examination of visual fields will avoid overlooking patients with

cortical blindness or visual neglect syndromes.

Chest pain or discomfort mimicking myocardial ischemia has been reported in patients with infarction of the thalamus, corona radiata, or lateral medulla (Gorson et al, 1996). In some of these patients, the sensory symptoms were part of a more extensive stroke syndrome, but the clinician should be aware of this possibility. Distal arm paresis with patterns of weakness conforming to peripheral nerve distributions may result from focal cerebral ischemia. Radial or ulnar involvement has been reported with small cortical infarction of the motor cortex (Gass et al, 2001). Again, abrupt onset and the presence of vascular risk factors should alert the astute clinician.

CONCLUSION

Timely and accurate diagnosis of acute ischemic stroke in the emergency setting relies on eliciting a focused history, performing an efficient, thorough, neurologic examination, and interpreting the results of laboratory and neuroimaging studies. The sudden onset of focal neurologic symptoms in a recognizable arterial distribution is the hallmark of stroke. Accurately determining time of symptom onset, measuring the severity of neurologic deficit, and excluding nonischemic causes of strokelike symptoms may lead to identification of patients eligible for acute stroke therapy. An efficient and systematic approach to stroke diagnosis facilitates evidence-based treatment.

REFERENCES

Adams HP Jr, Davis PH, Leira EC, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: a report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). Neurology 1999;53(1):126–131.

Adams HP Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists [published errata appear in Stroke 2007;38(6):e38 and Stroke 2007;38(9):e96]. Stroke 2007;38(6):1655–1711.

Barber PA, Demchuk AM, Hudon ME, et al. Hyperdense sylvian fissure MCA ''dot'' sign: A CT marker of acute ischemia. Stroke 2001;32(1):84–88.

Barber PA, Demchuck AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. Lancet 2000;355(9216):1670–1674.

Bastianello S, Pierallini A, Colonnese C, et al. Hyperdense middle cerebral artery CT sign. Comparison with angiography in the acute phase of ischemic supratentorial infarction. Neuroradiology 1991;33(3):207–211.

Besson G, Robert C, Hommel M, Perret J. Is it clinically possible to distinguish nonhemorrhagic infarct from hemorrhagic stroke? Stroke 1995;26(7):1205–1209.

Brott T, Adams HP Jr, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989;20(7):864–870.

Chalela JA, Kidwell CS, Nentwich LM, et al. Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison. Lancet 2007;369(9558):293–298.

Edlow JA, Caplan LR. Avoiding pitfalls in the diagnosis of subarachnoid hemorrhage. N Engl J Med 2000;342(1):29–36.

Ehsan T, Hayat G, Malkoff MD, et al. Hyperdense basilar artery. An early computed tomography sign of thrombosis. J Neuroimaging 1994;4(4):200–205.

Fiebach JB, Schellinger PD, Gass A, et al. Stroke magnetic resonance imaging is accurate in hyperacute intracerebral hemorrhage: a multicenter study on the validity of stroke imaging. Stroke 2004;35(2):502–506.

Fiebach JB, Schellinger PD, Jansen O, et al. CT and diffusion-weighted MR imaging in randomized order: diffusion-weighted imaging results in higher accuracy and lower interrater variability in the diagnosis of hyperacute ischemic stroke. Stroke 2002;33(9):2206–2210.

Fischer U, Arnold M, Nedeltchev K, et al. NIHSS score and arteriographic findings in acute ischemic stroke. Stroke 2005;36(10):2121–2125.

Gass A, Szabo K, Behrens S, et al. A diffusion-weighted MRI study of acute ischemic distal arm paresis. Neurology 2001;57(9):1589–1594.

Goldstein LB. Improving the clinical diagnosis of stroke. Stroke 2006;37(3):754–755.

Goldstein LB, Samsa GP. Reliability of the National Institutes of Health Stroke Scale: extension to non-neurologists in the context of a clinical trial. Stroke 1997;28(2):307–310.

Gorson KC, Pessin MS, DeWitt LD, et al. Stroke with sensory symptoms mimicking myocardial ischemia. Neurology 1996;46(2):548–551.

Grotta JC, Chiu D, Lu M, et al. Agreement and variability in the interpretation of early CT changes in stroke patients qualifying for intravenous rtPA therapy. Stroke 1999;30(8):1528–1533.

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(13):1017–1025.

Hand PJ, Kwan J, Lindley RI, et al. Distinguishing between stroke and mimic at the bedside: the brain attack study. Stroke 2006;37(3):769–775.

Hjort N, Christensen S, Solling C, et al. Ischemic injury detected by diffusion imaging 11 minutes after stroke. Ann Neurol 2005;58(3):462–465.

Huff JS. Stroke mimics and chameleons. Emerg Med Clin N Am 2002;20(3):583–595.

Kasner SE. Clinical interpretation and use of stroke scales. Lancet Neurol 2006;5(7):603–612.

Kidwell CS, Chalela JA, Saver JL, et al. Comparison of MRI and CT for detection of acute intracerebral hemorrhage. JAMA 2004;292(15):1823–1830.

Libman RB, Wirkowski E, Alvir J, Rao TH. Conditions that mimic stroke in the emergency department. Implications for acute stroke trials. Arch Neurol 1995;52(11):1119–1122.

Lyden P, Lu M, Jackson C, et al. Underlying structure of the National Institutes of Health Stroke Scale: results of a factor analysis. NINDS tPA Stroke Trial Investigators. Stroke 1999;30(11):2347–2354.

Mader TJ, Mandel A. A new clinical scoring system fails to differentiate hemorrhagic from ischemic stroke when used in the acute care setting. J Emerg Med 1998;16(1): 9–13.

Marler JR, Tilley BC, Lu M, et al. Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. Neurology 2000;55(11):1649–1655.

O'Brien PA, Ryder DQ, Twomey C. The role of computed tomography brain scan in the diagnosis of acute stroke in the elderly. Age Ageing 1987;16(5):319–322.

Patel MR, Edelman RR, Warach S. Detection of hyperacute primary intraparenchymal hemorrhage by magnetic resonance imaging. Stroke 1996;27(12):2321–2324.

Patel SC, Levine SR, Tilley BC, et al. Lack of clinical significance of early ischemic changes on computed tomography in acute stroke. JAMA 2001;286(22):2830–2838.

Sagar G, Riley P, Vohrah A. Is admission chest radiography of any clinical value in acute stroke patients? Clin Radiol 1996;51(7):499–502.

Sattin JA, Olson SE, Liu L, et al. An expedited code stroke protocol is feasible and safe. Stroke 2006;37(12):2935–2939.

Snyder H, Robinson K, Shah D, et al. Signs and symptoms of patients with brain tumors presenting to the emergency department. J Emerg Med 1993;11(3):253–258.

Tomsick TA, Brott TG, Olinger CP, et al. Hyperdense middle cerebral artery: incidence and quantitative significance. Neuroradiology 1989;31(4):312–315.

von Kummer R, Nolte PN, Schnittger H, et al. Detectability of cerebral hemisphere ischaemic infarcts by CT within 6 h of stroke. Neuroradiology 1996;38(1):31–33.

Wardlaw JM, Mielke O. Early signs of brain infarction at CT: observer reliability and outcome after thrombolytic treatment—systematic review. Radiology 2005;235(2):444–453.

Wiesmann M, Mayer TE, Yousry I, et al. Detection of hyperacute subarachnoid hemorrhage of the brain by using magnetic resonance imaging. J Neurosurg 2002;96(4):684–689.

Woo D, Broderick JP, Kothari RU, et al. Does the National Institutes of Health Stroke Scale favor left hemisphere strokes? NINDS t-PA Stroke Study Group. Stroke 1999;30(11):2355–2359.

PATHOPHYSIOLOGY OF ACUTE ISCHEMIC STROKE

Tudor G. Jovin, Andrew M. Demchuk, Rishi Gupta

ABSTRACT

In acute ischemic stroke, abrupt vessel occlusion results in a drop in regional CBF, leading to time-dependent compartmentalization of the ischemic brain into tissue that is irreversibly damaged (ischemic core), tissue that is functionally impaired but structurally intact and thus potentially salvageable (penumbra), and tissue that is hypoperfused but not threatened under normal circumstances (oligemic brain). At a cellular level, neuronal damage occurs through a complex interaction of mechanisms (necrosis, apoptosis, excitotoxicity, inflammation, peri-infarct depolarization, acidosis, and free radical formation) that are characteristic for each compartment. All these mechanisms are potential targets for neuroprotective therapy, which, combined with flow restoration strategies, is likely to improve outcome significantly in human stroke.

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INTRODUCTION

Acute ischemic stroke is characterized by abrupt neurologic dysfunction due to focal brain ischemia resulting in persistent neurologic deficit or accompanied by characteristic abnormalities on brain imaging (Albers et al, 2002).

Until recently, stroke was defined using clinical criteria alone, based on duration of symptoms lasting 24 hours or longer (Ad Hoc Committee, 1975). If the symptoms persisted for less than 24 hours, the condition was termed transient ischemic attack (TIA) However, modern neuroimaging techniques, especially diffusion MRI, have shown that defining stroke or TIA based only on duration of symptoms may not be accurate, since permanent brain damage can occur even when symptoms last only minutes (Ay et al, 1999; Engelter et al, 1999; Kidwell et al, 1999). Therefore, recently proposed definitions of TIA take into account both the duration of symptoms (typically less than an hour) and lack of acute infarction on brain imaging (Albers et al, 2002). Ovbiagele and colleagues (2003) estimated that adopting a definition of TIA based on the above criteria would reduce estimates of the annual incidence of TIA by 33% (currently estimated to be 180,000 annually) and increase annual number of strokes by 7% (currently estimated at 820,000 per year).

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Unlabeled Use of Products/Investigational Use Disclosure: Drs Jovin and Gupta have nothing to disclose. Dr Demchuk discusses the unlabeled use of emerging therapies with numerous references to potential therapies.

ETIOLOGIC AND PATHOLOGIC ASPECTS

It is important to recognize that ischemic stroke results from a heterogeneous group of disorders whose final common pathway leading to clinical manifestations is interruption of blood flow through vascular occlusion. This results in an infarct of which the size is dependent on extent, duration, and severity of ischemia. Brain infarcts resulting from arterial occlusion are divided based on their macroscopic appearance into white (bland) and red (hemorrhagic) infarcts (Garcia et al, 1998). By gross anatomy, the former are composed of few or no petechiae while the latter are characterized by grossly visible blood. This latter term is equivalent to hemorrhagic transformation, which refers to leaking of red blood cells into a dying and ischemic brain tissue, and should not be confused with parenchymal hematoma, which represents a homogenous collection of blood usually resulting from a ruptured blood vessel. Serial brain imaging studies in patients with acute stroke have demonstrated that hemorrhagic transformation of an initially bland infarct can occur in up to 80% of patients (Hart and Easton, 1986; Lyden and Zivin, 1993; Mayer et al, 2000). The risk of early hemorrhagic transformation and parenchymal hematoma is greatly increased by administration of thrombolytics or anticoagulants in acute ischemic stroke (Larrue et al, 1997).

Gross anatomy studies reveal that arterial infarcts evolve over several stages (Garcia et al, 1998). In the first 12 to 24 hours after the ictus, the lesion is barely visible to the naked eye. Swelling reaches its zenith at days 3 to 5; in large strokes this can become life threatening due to displacement and compression of neighboring structures. Between days 5 and 10, the infarcted brain becomes sharply demarcated from the unaffected brain tissue. The chronic stage, occurring weeks or months after the ictus, features a fluid-filled cavity that results from reabsorption of necrotic debris, hence the name liquefaction necrosis.

STROKE MECHANISMS

Two major mechanisms are responsible for ischemia in acute stroke: thromboembolism and hemodynamic failure. The former usually occurs as a result of embolism or in situ thrombosis and leads to an abrupt fall in regional cerebral blood flow (CBF). The latter usually occurs with arterial occlusion or stenosis, when collateral blood supply maintains CBF at levels that are sufficient for preservation of brain function under normal circumstances. In these cases, cerebral ischemia may be triggered by conditions that decrease perfusion proximally to the arterial lesion (systemic hypotension or low cardiac output) and increase metabolic demands (fever, acidosis) or conditions that lead to ''steal'' of blood from affected to unaffected areas in the brain (carbon dioxide retention) (Alexandrov et al, 2007). Strokes occurring through these mechanisms are located predominantly in the so-called borderzones or watershed regions, which are areas in the brain bordering major vascular territories such as the middle cerebral artery (MCA)/internal carotid artery or MCA/posterior cerebral artery interface (Klijn et al, 1997). Caplan and Hennerici (1998) postulated that embolism and hypoperfusion oftentimes coexist and potentiate each other. They proposed impaired clearance of emboli due to low flow states as a link between these two factors in the pathophysiology of brain infarction.

Embolism

Embolic material formed within the heart or vascular system travels through the arterial system, lodging in a vessel and partially or completely occluding it.

KEY POINTS

- Ischemic stroke results from a heterogeneous group of disorders whose final common pathway is interruption of blood flow through vascular occlusion.
- Two major mechanisms are responsible for ischemia in acute stroke: thromboembolism and hemodynamic failure.
- Embolism and hypoperfusion can coexist and potentiate each other.

KEY POINT

- The most common sources of emboli are the heart and large arteries.

The most common sources of emboli are the heart and large arteries. Other rare sources of emboli are air, fat, cholesterol, bacteria, tumor cells, and particulate matter from injected drugs (Caplan, 2000).

Cardioembolism. Cardioembolism accounts for 20% to 30% of all ischemic stroke (Grau et al, 2001; Kolominsky-Rabas et al, 2001; Petty et al, 2000; Sacco et al, 1995). **Table 2-1** outlines the high risk versus low or uncertain risk conditions for cardioembolic stroke (Ferro, 2003). Conditions considered at high risk for embolization to the brain are atrial fibrillation, sustained atrial flutter, sick sinus syndrome, left atrial thrombus, left atrial appendage thrombus, left atrial myxoma, mitral stenosis, prosthetic valve, infective endocarditis, noninfective endocarditis, left ventricular thrombus, left ventricular myxoma, recent anterior myocardial infarct, and dilated cardiomyopathy. Conditions considered at low or uncertain risk for brain embolization include patent foramen ovale, atrial septal aneurysm, spontaneous atrial contrast, mitral annulus calcification, mitral valve prolapse, calcified aortic stenosis, fibroelastoma, giant Lambl excrescences, akinetic or dyskinetic ventricular wall segment, subaortic hypertrophic cardiomyopathy, and congestive heart failure (Marchal et al, 1999).

Artery-to-artery embolism. Emboli occluding brain arteries can also originate from large vessels situated more proximally, such as the aorta, extracranial carotid, or vertebral arteries or intracranial arteries. In these circumstances, the embolic material is composed of clot, platelet aggregates or plaque debris that usually breaks off from atherosclerotic plaques (Furlan et al, 1996). This is a major mechanism responsible for stroke due to large vessel atherosclerosis, which accounts for 15% to 20% of all ischemic strokes (Grau et al, 2001; Kolominsky-Rabas

TABLE 2-1 High Risk Versus Low or Uncertain Risk Conditions for Cardioembolic Stroke

▶ **High Risk Conditions**
Atrial fibrillation
Sustained atrial flutter
Sick sinus syndrome
Left atrial thrombus
Left atrial appendage thrombus
Left atrial myxoma
Mitral stenosis
Mechanical valve
Infective endocarditis
Noninfective endocarditis
Left ventricular myxoma
Recent anterior myocardial infarct
Dilated cardiomyopathy
▶ **Low or Uncertain Risk Condition**
Patent foramen ovale
Atrial septal aneurysm
Spontaneous atrial contrast
Mitral valve prolapse
Calcified aortic stenosis
Fibroelastoma
Giant Lambel excrescence
Akinetic or dyskinetic ventricular wall segment
Subaortic hypertrophic cardiomyopathy
Congestive heart failure

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et al, 2001; Petty et al, 2000; Sacco et al, 1995).

Thrombosis

Thrombosis represents an obstruction of flow with thrombus formation resulting from an occlusive process initiated within the vessel wall. In the vast majority of cases this is caused by atherosclerotic disease, hence the name atherothrombosis. Less common vascular pathologies leading to vessel stenosis or occlusion include arterial dissection (intracranial or extracranial), fibromuscular dysplasia, vasospasm (drug induced, inflammatory, or infectious), radiation-induced vasculopathy, extrinsic compression such as tumor or other mass lesion, or moyamoya disease.

Small vessel disease. Thrombotic occlusion of the small penetrating arteries in the brain is another important cause of strokes, accounting for another approximately 20% to 30% of all ischemic strokes. This type of vascular lesion is strongly associated with hypertension and is characterized pathologically by lipohyalinosis, microatheroma, fibrinoid necrosis, and Charcot-Bouchard aneurysms (Bamford and Warlow, 1988; Fisher, 1982; Fisher, 1998; Mohr, 1982). Lipohyalinosis is characterized by replacement of the normal vessel wall with fibrin and collagen and is specifically associated with hypertension. Microatheroma represents an atheromatous plaque of the small vessel that may involve the origin of a penetrating artery (Caplan, 1989). This latter mechanism is believed to be responsible for larger subcortical infarcts. Fibrinoid necrosis is usually associated with extremely high blood pressure, leading to necrosis of smooth muscle cells and extravasation of plasma proteins, which appear microscopically as fine granular eosinophilic deposits in the connective tissue of the vessel wall. Charcot-Bouchard aneurysms are areas of focal dilatation in the small vessel wall, which may thrombose, leading to vessel occlusion.

CEREBRAL BLOOD FLOW CHANGES

Introduction

Following vessel occlusion, the main factors ultimately determining tissue outcome are regional CBF and duration of vessel occlusion. A decrease in regional CBF leads to diminished tissue perfusion. In persistent large vessel occlusion, local perfusion pressure, which is the main factor influencing the eventual outcome of tissue (Baron, 2001), depends on several factors such as the presence and extent of collaterals and systemic arterial pressure (due to loss of the ischemic brain's autoregulatory capacity). It is inversely correlated to the local tissue pressure (which is increased by ischemic edema).

Cerebral Blood Flow Thresholds in Acute Cerebral Ischemia

The difference in tissue outcome following arterial occlusion is based on the concept that CBF thresholds exist, below which neuronal integrity and function are differentially affected (**Figure 2-1**). Early human studies performed in the 1950s during carotid artery clamping for carotid endarterectomy using intracarotid xenon 133 injections (Boysen, 1971; Jennett et al, 1966) reported that hemiparesis occurred when regional CBF fell below 50% to 30% of normal, and permanent neurologic deficit occurred if mean CBF fell below 30% of normal. Evidence also indicated that development of permanent neurologic sequelae is a time-dependent process; for any given blood flow level, low CBF values are tolerated only for a short period of time, while higher CBF values require longer time for infarction to occur. Several investigators (Sundt et al, 1974; Trojaborg and Boysen, 1973) have

KEY POINTS

- Thrombosis is associated with thrombus formation as a consequence of an occlusive process initiated within the vessel wall and is usually caused by atherosclerotic disease.
- Occlusive disease of small penetrating arteries in the brain (small vessel disease) accounts for 20% to 30% of ischemic strokes.
- Following vessel occlusion, the main factors ultimately determining tissue outcome are regional cerebral blood flow and duration of vessel occlusion.
- The difference in tissue outcome following arterial occlusion is based on the concept that cerebral blood flow thresholds exist, below which neuronal integrity and function are differentially affected.

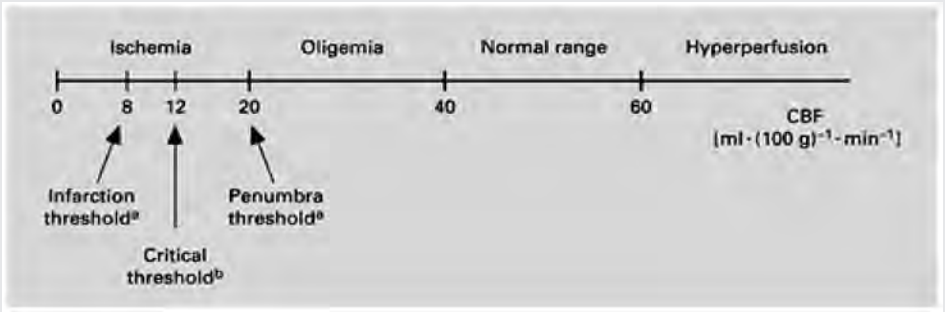

FIGURE 2-1 Schematic drawing of the different cerebral blood flow thresholds in man.

[a]Furlan M, Marchal G, Viader F, et al. Spontaneous neurological recovery after stroke and the fate of the ischemic penumbra. Ann Neurol 1996;40(2):216–226.
Marchal G, Beaudouin V, Rioux P, et al. Prolonged persistence of substantial volumes of potentially viable brain tissue after stroke. Stroke 1996;27(4):599–606.
Marchal G, Benali K, Iglésias S, et al. Voxel-based mapping of irreversible ischaemic damage with PET in acute stroke. Brain 1999;122(pt 12):2387–2400.
[b]Heiss WD, Grond M, Thiel A, et al. Tissue at risk of infarction rescued by early reperfusion: A positron emission tomography study in systemic recombinant tissue plasminogen activator thrombolysis of acute stroke. J Cereb Blood Flow Metab 1998;18(12):1298–1307.
Heiss WD, Thiel A, Grond M, Graf R. Which targets are relevant for therapy of acute ischemic stroke? Stroke 1999;30(7):1486–1489.

Baron JC. Perfusion thresholds in human cerebral ischemia: historical perspective and therapeutic implications. Cerebrovasc Dis 2001;11(suppl 1):2–8. Reprinted with permission from S. Karger, AG, Basel.

studied the relationship between EEG changes and regional CBF during carotid clamping. EEG would slow down when mean CBF fell below 23 mL/100 g/min, while at values below 15 mL/100 g/min the EEG would become flat.

The concept of CBF threshold in focal cerebral ischemia proposed by these early human studies was then reinforced by landmark studies performed by Symon and colleagues (1977), who investigated the relationship between severity of local CBF impairment and degree of neurologic dysfunction at various durations of ischemia in a baboon model of MCA occlusion. Symon and colleagues (1977) demonstrated that brain tissue perfuses between certain CBF values (22 mL/100 mg/min to 8 mL/100 mg/min) even when prolonged hypoperfusion stops functioning, but maintains its structural integrity and, most importantly, can be salvaged with reperfusion. **Figure 2-2** depicts a summary of metabolic and electrophysiologic disturbances according to reductions of cortical blood flow at different thresholds.

The time dependence of ischemic thresholds in producing permanent or transient neurologic damage has been demonstrated by Jones and colleagues (1981) in primate studies using a temporary or permanent MCA occlusion model. These experiments demonstrated that the CBF values below which brain tissue becomes infarcted are dependent on the duration of vessel occlusion. Two hours of continuous MCA occlusion in awake macaque monkeys required CBF values of 5 mL/100 g/min to produce infarction, while 3 hours of continuous occlusion resulted in infarction if CBF values were 12 mL/100 mg/min or less. Permanent occlusion resulted in infarction if flows were 18 mL/100 mg/min or less. It should be noted that 30 minutes of occlusion did not result in infarction even at CBF values below 5 mL/100 mg/min.

It is important to understand that the blood flow thresholds studied in most animal and human experiments refer to ischemic tolerance of the brain cortex. Thresholds for deep white

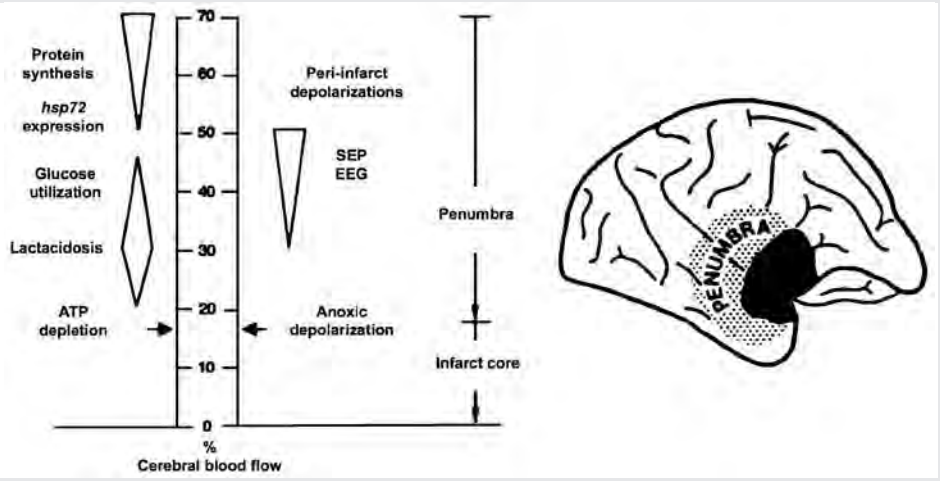

FIGURE 2-2 Thresholds of metabolic (*left*) and electrophysiologic (*right*) disturbances during gradual reduction of cortical blood flow.

SEP = somatosensory evoked potentials; EEG = electroencephalogram; ATP = adenosine triphosphate.

Hossmann KA. Pathophysiology and therapy of experimental stroke. Cell Mol Neurobiol 2006;26(7–8):1057–1083. Reprinted with permission from Springer Science and Business Media.

KEY POINTS

- The ischemic core represents tissue that is irreversibly damaged.
- The ischemic penumbra represents tissue that is functionally impaired but structurally intact and, as such, potentially salvageable. Salvaging this tissue by restoring its flow to nonischemic levels is the aim of reperfusion therapy in acute stroke.

matter or basal ganglia have not been studied rigorously and are simply unknown. It is believed, however, that gray matter is more susceptible to infarction than white matter, and that within the gray matter the basal ganglia have a lower ischemic tolerance than the cortex (Marcouz et al, 1982).

Concept of Ischemic Core and Ischemic Penumbra

The notion that in acute stroke, depending on the extent and duration of hypoperfusion, the tissue supplied by the occluded artery is compartmentalized into areas of irreversibly damaged brain tissue and areas of brain tissue that are hypoperfused but viable led to the concept of ischemic core and ischemic penumbra proposed by Astrup and colleagues (1981). The ischemic core represents tissue that is irreversibly damaged. PET studies in humans suggest that beyond a certain time limit (probably no longer than an hour) the ischemic core corresponds to CBF values of less than 7 mL/100 mg/min (Furlan et al, 1996; Marchal et al, 1996; Marchal et al, 1999) to 12 mL/100 mg/min (Heiss, 2000; Heiss et al, 2001b). The ischemic penumbra represents tissue that is functionally impaired but structurally intact and, as such, potentially salvageable. It corresponds to a high CBF limit of 17 mL/100 mg/min to 22 mL/100 mg/min and a low CBF limit of 7 mL/100 mg/min to 12 mL/100 mg/min. Salvaging this tissue by restoring its flow to nonischemic levels is the aim of acute stroke therapy. Another compartment, termed by Symon and colleagues (1977) *oligemia*, represents mildly hypoperfused tissue from the normal range down to around 22 mL/100 mg/min. It is believed that under normal circumstances this tissue is not at risk of infarction (Baron, 2001). It is conceivable, however, that under certain circumstances, such as hypotension, fever, or acidosis, oligemic tissue can be incorporated into penumbra and subsequently undergo infarction.

Evidence in the literature suggests that there is temporal evolution of the core, which grows at the expense of

penumbra (Ginsberg, 2003; Heiss et al, 2001a; Raichle, 1982) (**Figure 2-3**). This process occurs because of the interaction of a multitude of complex factors acting concomitantly or sequentially (Hossmann, 2006). It is known that the ischemic penumbra represents a dynamic phenomenon that evolves in space and time. If vessel occlusion persists, the penumbra may shrink because of progressive recruitment into the core. Alternatively, it may return to a normal state following vessel recanalization or possibly neuroprotective interventions. It thus appears that the ischemic penumbra represents a transitional state between evolution into permanent ischemia as one possibility and transformation into normal tissue as the other possibility. On the basis of a rat model of MCA occlusion studied in a multimodal fashion assessing CBF, metabolism, and gene expression, Ginsberg (2003) concluded that the penumbra lies within a narrow range of perfusion and thus is precariously dependent on small perfusion pressure changes; that the penumbra is electrophysiologically dynamic and undergoes recurrent depolarizations; and that it is metabolically unstable, being

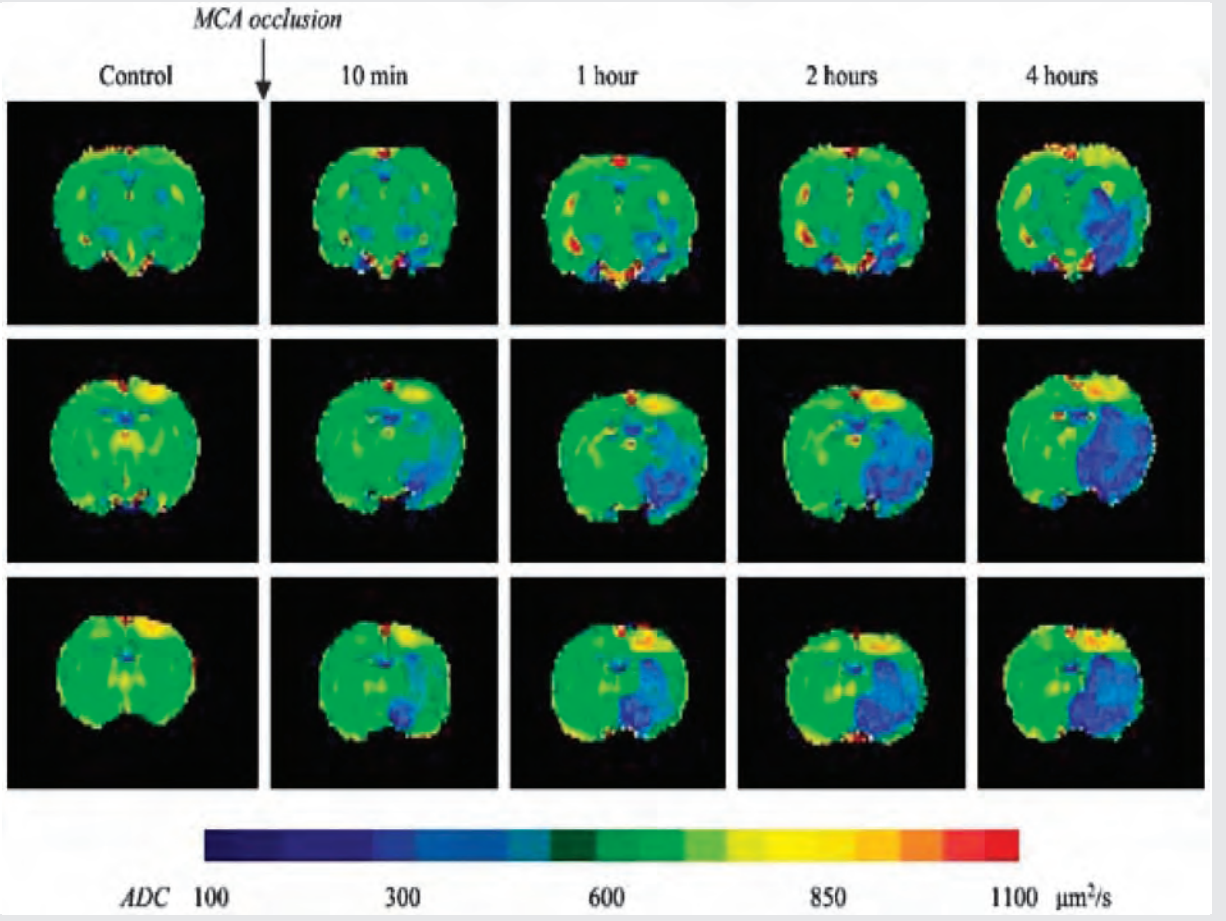

FIGURE 2-3 Experimental model of middle cerebral artery occlusion in rats. Serial MRIs (coronal sections) at three levels in the brain depicting the apparent diffusion coefficient of water (ADC) (*blue*) demonstrating the time-dependent growth of the ischemic core.

Hossmann KA. Pathophysiology and therapy of experimental stroke. Cell Mol Neurobiol 2006;26(7–8):1057–1083. Reprinted with permission from Springer Science and Business Media.

the site of severe metabolism/flow dissociation.

Restriction of acute stroke therapy aimed at vessel recanalization to 3 hours from onset of symptoms for IV thrombolysis and 6 hours for intraarterial thrombolysis is based on the concept that the ischemic penumbra has a short lifespan, being rapidly incorporated into the core within hours of the ictus (Heiss et al, 2001b; Kaufman et al, 1999). Recent evidence suggests, however, that penumbral brain tissue of significant extent is present even beyond 6 hours of stroke onset. PET studies using quantitative CBF assessment (Furlan et al, 1996; Marchal et al, 1999) or markers of tissue hypoxia such as 18F fluoromisonidazole (Read et al, 2000) to assess penumbra, included patients studied within 6 hours to as late as 51 hours after stroke onset and reported the existence of penumbra comprising 30% to 45% of the total ischemic tissue at risk. Several investigators have estimated the penumbra based on diffusion/perfusion MRI (diffusion-weighted imaging [DWI]/perfusion-weighted imaging [PWI]) mismatch in acute stroke (Hjort et al, 2005; Schlaug et al, 1999). Since the diffusion abnormalities are presumed to represent an approximation of the irreversible ischemic lesion and the perfusion abnormalities are presumed to represent the brain territory at risk, the area of mismatch between DWI and PWI is considered a territory still viable but at risk of undergoing infarction and corresponds theoretically to the concept of ischemic penumbra. The major shortcoming of this concept derives from the lack of quantitative data provided by MRI imaging. It has been shown that the DWI lesion is not precise in distinguishing between irreversible and reversible ischemia (Guadagno et al, 2005). It incorporates both types of ischemia and therefore cannot be considered equivalent to the ischemic core (Guadagno et al, 2004; Guadagno et al, 2005; Sobesky et al, 2005). Additionally, the PWI lesion has been shown to incorporate both imminently threatened brain and brain that will not undergo infarction as a consequence of persistent vessel occlusion (Heiss et al, 2004). Since, by definition, penumbra represents tissue that will undergo infarction with continuous vessel occlusion, assessment of penumbral extent based on perfusion MRI is also not precise.

Using MRI technology, Schlaug and colleagues (1999) demonstrated that penumbra comprises about 40% of the total ischemic territory in a cohort of patients that was studied within 24 hours of symptom onset. Similar extent of penumbral volumes has been reported by numerous other investigators (Barber et al, 1999; Rordorf et al, 1998; Schellinger et al, 2001; Staroselskaya et al, 2001). These reports have also described that the presence of diffusion/perfusion mismatch is highly correlated with the presence of large vessel (internal carotid artery, MCA, or major division) occlusion. SPECT studies performed acutely in patients with large vessel occlusion have confirmed these findings (Ogasawara et al, 2000; Ueda et al, 1999). Insights into the pathophysiology of acute stroke as it relates to reversible versus irreversible brain tissue are provided by a study in which a homogenous group of patients with stroke due to angiographically proven M1 MCA occlusion were studied within 6 hours of symptom onset with xenon-CT-CBF technology (Jovin et al, 2003). This study, in which core and penumbra were determined based on established perfusion thresholds, indicated that within this time frame, irrespective of the point in time at which the patients were studied, the ischemic penumbra was consistently present and relatively constant, comprising

KEY POINTS

- At a cellular level, the biochemical and electrophysiologic mechanisms involved in the ischemic brain injury vary according to the extent of cerebral ischemia.
- Neuronal cell death occurs as a result of two main mechanisms: necrosis and apoptosis.
- Necrosis occurs predominantly in the hyperacute stage within the ischemic core. It occurs mainly as a consequence of disruption of cellular homeostasis due to energy failure and is accompanied by cellular swelling, membrane lysis, inflammation, vascular damage, and edema formation.

approximately one-third of the MCA territory. In contrast to the penumbra, the ischemic core was highly variable, ranging from 20% to 70% of cortical MCA territory. The authors found that both in patients who recanalized and in those who did not recanalize, the extent of core and not that of penumbra was correlated with clinical outcome.

CELLULAR MECHANISMS OF ISCHEMIC NEURONAL INJURY IN ACUTE STROKE

Introduction

At a cellular level, the biochemical and electrophysiologic mechanisms involved in the ischemic brain injury vary according to the extent of cerebral ischemia. Neuronal cell death occurs as a result of two main mechanisms: necrosis and apoptosis. Necrosis is a process that is not regulated or programmed and is the predominant mechanism that follows acute permanent focal vascular occlusion. Necrosis occurs mainly as a consequence of disruption of cellular homeostasis due to energy failure and is accompanied by cellular swelling, membrane lysis, inflammation, vascular damage, and edema formation (Bhardwaj et al, 2003) (**Figure 2-4**). Apoptosis, or programmed cell death, is characterized by cell shrinkage, chromatin clumping, and cytoplasmic blebbing and is not associated with inflammation or secondary injury to surrounding brain (Graham and Chen, 2001; Thompson, 1995; Vaux et al, 1994) (**Figure 2-5**). These two distinct types of neuronal death appear to represent opposite poles of a spectrum that coexist within the ischemic brain, with necrosis being the main mechanism of neuronal injury in the ischemic core and apoptosis being the main mechanism of neuronal injury in the penumbra where, because of the milder degree of ischemia, sufficient energy is produced to allow for expression of new proteins that mediate apoptosis (Bhardwaj et al, 2003; Dirnagl et al, 1999; Graham and Chen, 2001).

Acute vascular occlusion triggers a complex sequence of pathophysiologic events that evolve over time and space. Major pathogenic mechanisms of the ischemic cascade leading to neuronal injury constitute active targets for various neuroprotective strategies and include cytotoxicity, peri-infarct depolarization, inflammation, tissue acidosis, nitric oxide, and free radical production, as well as, at a later stage, apoptosis (Barber et al, 2003; Doyle et al, 2008; Dirnagl et al, 1999).

Excitotoxicity, Peri-infarct Depolarizations, Acidosis, Inflammation

The reduction in regional CBF through insufficient delivery of the neuron's main energy substrates, oxygen and glucose, results in inadequate production of energy required to maintain ionic gradients (Martin et al, 1994). Since the transport of calcium from the cell into the extracellular space is an energy-dependent process, this leads to intracellular accumulation of calcium. Calcium influx is further enhanced by impairment in the energy-dependent reuptake of excitatory amino acids, especially glutamate, and by release of excitatory amino acids into the extracellular space. An increase in extracellular glutamate leads to increased calcium influx, through increased stimulation of the NMDA or non-NMDA (mainly α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid [AMPA]) receptor (Budd, 1998). At the same time, sodium and chloride enter the neuron via channels for monovalent ions (Tyson et al, 1996). Water follows osmotic gradients, leading to edema, which is predominantly cytotoxic and can further diminish perfusion in regions surrounding the core, leading to

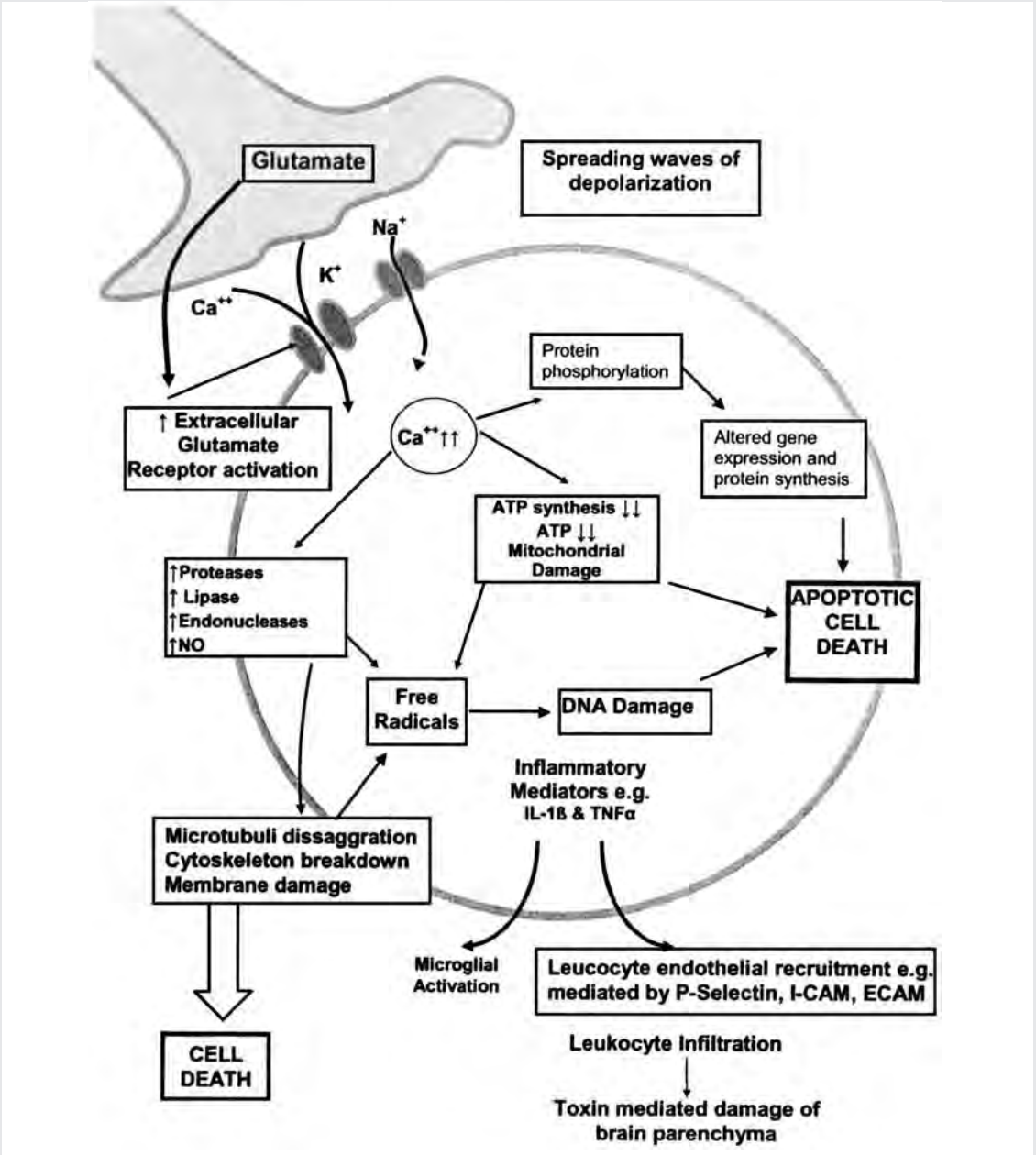

FIGURE 2-4 Cellular mechanisms of ischemic neuronal injury in acute stroke.

IL-1β = interleukin 1β; TNFα = tumor necrosis factor-α; ICAM = intercellular adhesion molecule; ECAM = endothelial cell adhesion molecule.

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recruitment of penumbral areas into the core (Hossmann, 2006; Raichle, 1982). Effects of delayed edema formation (at this stage predominantly vasogenic) include increased intracranial pressure, shift and displacement of brain structures, vascular compression, and herniation (Hossmann, 2006).

The accumulation of intracellular calcium leads to a series of events at both the cytoplasmic and nuclear levels that result in cell death through several

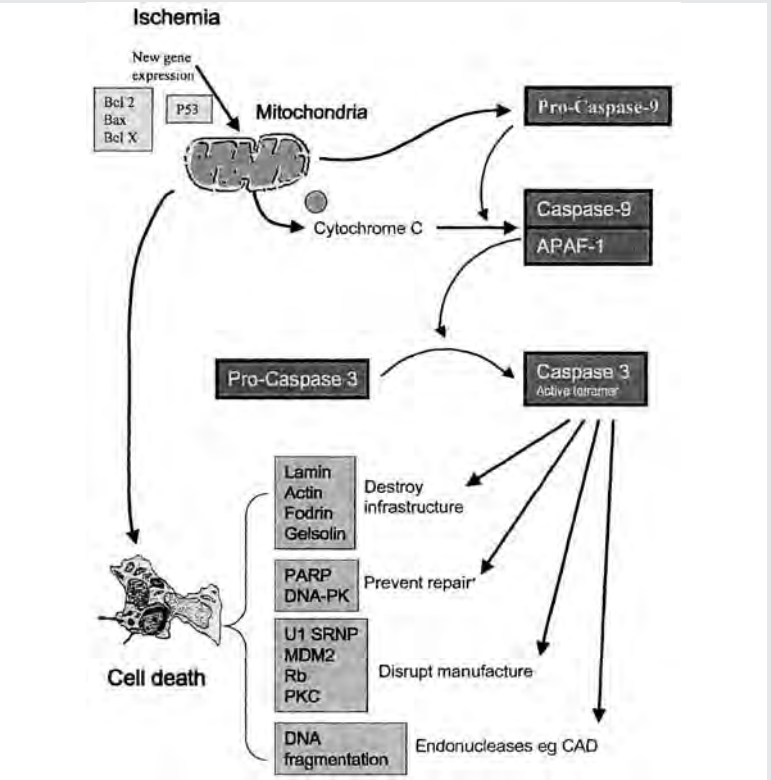

FIGURE 2-5 Overview of molecular events involved in apoptosis. PKC = protein kinase C; CAD = capase activated DNAase.

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mechanisms: activation of enzymes that degrade cytoskeletal proteins (Baudry et al, 1981; Chen and Strickland, 1997), activation of lipoxygenase and cyclooxygenase, xanthine oxydase and nitric oxide synthase with resultant accumulation of highly cytotoxic oxygen free radicals oxygen (O_2•), hydrogen peroxide (H2O2), hydroxyl (OH•), and nitric oxide (NO•). These reactions occur both in the cytoplasm and in the mitochondria. Mitochondria are an important source of reactive oxygen species. As a consequence of free radical–mediated disruption of the inner mitochondrial membrane and the oxidation of the proteins that mediate electron transport (Dugan and Choi, 1994), the mitochondrial membrane becomes leaky through the formation of a so-called mitochondrial permeability transition pore in the mitochondrial membrane (Mergenthaler et al, 2004). This results in mitochondrial swelling, intramitochondrial calcium accumulation, impaired energy production, and reactive oxygen species production (Kristian and Siesjo, 1998). Another consequence of disrupted mitochondrial permeability is the release of proapoptotic molecules, such as cytochrome *c* and caspase-9 (Dirnagl et al, 1999; Doyle et al, 2008).

Following energy loss, membrane potentials cannot be maintained, leading to depolarization of neurons and glia (Dirnagl et al, 1999). While in the core region depolarization may be permanent, in the penumbral area cells can depolarize and then undergo repetitive depolarization, an active energy-requiring

process. This so-called peri-infarct depolarization contributes to the increase in size of the infarct by further depleting energy reserves (Back et al, 1996; Doyle et al, 2008; Hossmann, 1996).

Acidosis, arising during ischemia, enhances brain damage through several mechanisms, such as edema formation, accumulation of hydrogen ions in the cell, inhibition of lactate oxidation, and impairment of mitochondrial respiration (Barber et al, 2003). On the other hand, acidosis appears to have antiexcitotoxic effects, and therefore some authors argue that the role of acidosis in focal cerebral ischemia is complex and poorly understood (Mergenthaler et al, 2004).

Inflammation further exacerbates the ischemic injury. Soon after onset of ischemia, astrocytes, microglia, endothelial cells, and leukocytes are activated. Peripherally derived leukocytes, such as polymorphonuclear leukocytes, T lymphocytes, and natural killer cells, also accumulate in the ischemic tissue (Clark et al, 1993a; Clark et al, 1993b; Ritter et al, 2000).

The accumulation of inflammatory cells in the ischemic lesion occurs as a result of intracellular calcium accumulation, increase in oxygen free radicals, as well as hypoxia itself (Dirnagl et al, 1999) and appears to be mediated through adhesion molecules such as integrins, selectins, and immunoglobulins (Doyle et al, 2008). Activation of inflammatory cells in the ischemic lesion results in the production of cytokines (Rothwell, 1997), such as tumor necrosis factor-α, interleukin-6, and interleukin-1. The last exacerbates the ischemic injury through fever, arachidonic acid release, enhancement of NMDA-mediated excitotoxicity, and stimulation of nitric oxide synthesis (Doyle et al, 2008).

Another deleterious effect of cytokines is the enhanced expression of adhesion molecules on the endothelial cell surface, including intercellular adhesion molecule-1, P selectin, and E selectin (Doyle et al, 2008; Gong et al, 1998; Lindsberg et al, 1991; Mergenthaler et al, 2004; Zhang et al, 1998). As a consequence, more neutrophils, and, later, macrophages and monocytes, adhere to the endothelium, cross the vascular wall, and enter the brain parenchyma. Microvascular obstruction by neutrophils can aggravate the degree of ischemia (del Zoppo et al, 1991) through worsening of microvascular perfusion. This phenomenon is similar to the no-reflow phenomenon known from the cardiology literature and may explain why, in some instances, tissue perfusion fails to improve significantly despite proximal vessel recanalization (Doyle et al, 2008). Other deleterious effects of inflammation on ischemic tissue include production of toxic mediators (oxygen free radicals, toxic prostanoids, tumor necrosis factor-α) by activated inflammatory cells and facilitation of apoptosis (Iadecola et al, 1997).

Apoptosis (Programmed Cell Death)

Apoptosis represents the predominant mechanism of neuronal damage in milder ischemic injury. It is characterized by an ordered and tightly controlled set of changes in gene expression and protein activity that results in neuronal cell death (Graham and Chen, 2001). A central role in apoptosis-mediated mechanisms of ischemic injury is attributed to genes that suppress or promote cell death and to a family of aspartate-specific cysteine proteases called caspases, of which 14 different enzymes have, to date, been described (Graham and Chen, 2001). These enzymes are protein cleaving and ultimately lead to destruction of key intracellular proteins with resultant cell disassembly and death.

Genes that control apoptosis include those that prevent cell death,

KEY POINT

- Apoptosis is the main mechanism of neuronal injury in the penumbra where, because of the milder degree of ischemia, sufficient energy is produced to allow for expression of new proteins that mediate cell death through an ordered and tightly controlled set of changes in gene expression and protein activity.

such as *BCL2*, and genes that promote cell death, such as *BAX* or p53. The main sites at which apoptosis can be initiated are the mitochondria, cell membrane receptors, and chromosomal DNA. Mitochondrial injury may result in release of cytochrome *c*, leading to activation of apoptosis through caspase-dependent mechanisms. However, a caspase-independent mechanism may also initiate apoptosis at the mitochondrial level (Green and Read, 1998). DNA damage can trigger apoptosis by inducing expression of the transcription factor p53 (Miyashita et al, 1994). This leads to alteration of transcription of several genes (including *BAX)* and in the initiation of apoptosis.

Blood-Brain Barrier and the Neurovascular Unit

The integrity of the blood-brain barrier plays an important role in the pathophysiology of acute stroke. Cellular elements that form the blood-brain barrier matrix include endothelial cells and astrocytes. During cerebral ischemia, the normal structure of this matrix and its intercellular signal exchange are affected by the ischemic process. A prominent role in the changes underlying blood-brain barrier dysfunction is attributed to a family of proteases called matrix metalloproteases (Lo, 2008; Mergenthaler et al, 2004). Increased presence of these enzymes, especially metalloproteinase-9, has been correlated with damage to the blood-brain barrier, with an increased risk of hemorrhagic transformation after tissue plasminogen activator (t-PA) administration and with the extent of neuronal damage (Mergenthaler et al, 2004).

An emerging concept in the pathophysiology of acute stroke is that of the neurovascular unit comprising endothelium and astrocytes in addition to the neuron (Lo, 2008; Lo et al, 2005). While, traditionally, stroke has been seen as primarily a neuronal disorder, the interaction between neurons, endothelium, and astrocytes through cell-cell signaling and cell-matrix interactions is regarded as increasingly important in the understanding of stroke and its response to stroke treatments (Lo, 2008).

REFERENCES

Ad Hoc Committee. Advisory Council for the National Institute of Neurological and Communicative Disorders and Stroke. A classification and outline of cerebrovascular diseases. II. Stroke 1975;6(5):564–616.

Albers GW, Caplan LR, Easton JD, et al. Transient ischemic attack—proposal for new definition. N Engl J Med 2002;347(21):1713–1716.

Alexandrov AV, Sharma VK, Lao AY, et al. Reversed Robin Hood syndrome in acute ischemic stroke patients. Stroke 2007;38(11):3045–3048.

Astrup J, Siesjo BK, Symon L. Thresholds in cerebral ischemia—the ischemic penumbra. Stroke 1981;12(6):723–725.

Ay H, Buonanno FS, Rordorf G, et al. Normal diffusion-weighted MRI during stroke-like deficits. Neurology 1999;52(9):1784–1792.

Back T, Ginsberg MD, Dietrich WD, Watson BD. Induction of spreading depression in the ischemic hemisphere following experimental middle cerebral artery occlusion: effect on infarct morphology. J Cereb Blood Flow Metab 1996;16(2):202–213.

Bamford JM, Warlow CP. Evolution and testing of the lacunar hypothesis. Stroke 1988;19(9):1074–1082.

Barber PA, Davis SM, Darby DG, et al. Absent middle cerebral artery flow predicts the presence and evolution of the ischemic penumbra. Neurology 1999;52(6): 1125–1132.

Barber PA, Demchuk AM, Hirt L, Buchan AM. Biochemistry of ischemic stroke. In: Barnett HJM, Bogousslavsky J, Meldrum H, eds. Advances in neurology: ischemic stroke. Philadelphia: Lippincott Williams & Willkins, 2003:151.

Baron JC. Perfusion thresholds in human cerebral ischemia: historical perspective and therapeutic implications. Cerebrovasc Dis 2001;11(suppl 1):2–8.

Baudry M, Bundman MC, Smith EK, Lynch GS. Micromolar calcium stimulates proteolysis and glutamate binding in rat brain synaptic membranes. Science 1981; 212(4497):937–938.

Bhardwaj A, Alkayed NJ, Kirsch JR, Hurn PD. Mechanisms of ischemic brain damage. Curr Cardiol Rep 2003;5(2):160–167.

Boysen G. Cerebral blood flow measurement as a safeguard during carotid endarterectomy. Stroke 1971;2(1):1–10.

Budd SL. Mechanisms of neuronal damage in brain hypoxia/ischemia: focus on the role of mitochondrial calcium accumulation. Pharmacol Ther 1998;80(2): 203–229.

Caplan LR. Intracranial branch atheromatous disease: a neglected, understudied, and underused concept [published errata appears in Neurology 1990;40(4):725]. Neurology 1989;39(9):1246–1250.

Caplan LR. Basic pathology, anatomy, and pathophysiology of stroke. In: Caplan's stroke: a clinical approach. Boston: Butterworth-Heinemann, 2000:19.

Caplan LR, Hennerici M. Impaired clearance of emboli (washout) is an important link between hypoperfusion, embolism, and ischemic stroke. Arch Neurol 1998;55(11):1475–1482.

Chen ZL, Strickland S. Neuronal death in the hippocampus is promoted by plasmin-catalyzed degradation of laminin. Cell 1997;91(7):917–925.

Clark RK, Lee EV, Fish CJ, et al. Development of tissue damage, inflammation and resolution following stroke: an immunohistochemical and quantitative planimetric study. Brain Res Bull 1993a;31(5):565–572.

Clark WM, Coull BM, Briley DP, et al. Circulating intercellular adhesion molecule-1 levels and neutrophil adhesion in stroke. J Neuroimmunol 1993b;44(1):123–125.

del Zoppo GJ, Schmid-Schonbein GW, Mori E, et al. Polymorphonuclear leukocytes occlude capillaries following middle cerebral artery occlusion and reperfusion in baboons. Stroke 1991;22(10):1276–1283.

Dirnagl U, Iadecola C, Moskowitz MA. Pathobiology of ischaemic stroke: an integrated view. Trends Neurosci 1999;22(9):391–397.

Doyle KP, Simon RP, Stenzel-Poore MP. Mechanisms of ischemic brain damage [published online ahead of print January 25, 2008]. Neuropharmacology PMID: 18308346.

Dugan LL, Choi DW. Excitotoxicity, free radicals, and cell membrane changes. Ann Neurol 1994;35(suppl):S17–S21.

Engelter ST, Provenzale JM, Petrella JR, Alberts MJ. Diffusion MR imaging and transient ischemic attacks. Stroke 1999;30(12):2762–2763.

Ferro JM. Cardioembolic stroke: an update. Lancet Neurol 2003;2(3):177–188.

Fisher CM. Lacunar strokes and infarcts: a review. Neurology 1982;32(8):871–876.

Fisher CM. Lacunes: small, deep cerebral infarcts. 1965. Neurology 1998;50(4):841–852.

Furlan M, Marchal G, Viader F, et al. Spontaneous neurological recovery after stroke and the fate of the ischemic penumbra. Ann Neurol 1996;40(2):216–226.

Garcia JH, Ho K, Pantoni L. Pathology. In: Barnett HJM, Mohr JP, Stein BM, Yatsu FM, editors. Stroke pathophysiology, diagnosis and management. 3rd ed. Philadelphia: Churchill Livingstone, 1998:147–148.

Ginsberg MD. Adventures in the pathophysiology of brain ischemia: penumbra, gene expression, neuroprotection: the 2002 Thomas Willis Lecture. Stroke 2003;34(1):214–223.

Gong C, Qin Z, Betz AL, et al. Cellular localization of tumor necrosis factor alpha following focal cerebral ischemia in mice [published errata appears in Brain Res 1999;818(1):184]. Brain Res 1998;801(1–2):1–8.

Graham SH, Chen J. Programmed cell death in cerebral ischemia. J Cereb Blood Flow Metab 2001;21(2):99–109.

Grau AJ, Weimar C, Buggle F, et al. Risk factors, outcome, and treatment in subtypes of ischemic stroke: the German stroke data bank. Stroke 2001;32(11):2559–2566.

Green DR, Read JC. Mitochondria and apoptosis. Science 1998;281(5381):1309–1312.

Guadagno JV, Warburton EA, Aigbirhio FI, et al. Does the acute diffusion-weighted imaging lesion represent penumbra as well as core? A combined quantitative PET/MRI voxel-based study. J Cereb Blood Flow Metab 2004;24(11):1249–1254.

Guadagno JV, Warburton EA, Jones PS, et al. The diffusion-weighted lesion in acute stroke: heterogeneous patterns of flow/metabolism uncoupling as assessed by quantitative positron emission tomography. Cerebrovasc Dis 2005;19(4):239–246.

Hart RG, Easton JD. Hemorrhagic infarcts. Stroke 1986;17(4):586–589.

Heiss WD. Ischemic penumbra: evidence from functional imaging in man. J Cereb Blood Flow Metab 2000;20(9):1276–1293.

Heiss WD, Forsting M, Diener HC. Imaging in cerebrovascular disease. Curr Opin Neurol 2001a;14(1):67–75.

Heiss WD, Kracht LW, Thiel A, et al. Penumbral probability thresholds of cortical flumazenil binding and blood flow predicting tissue outcome in patients with cerebral ischaemia. Brain 2001b;124(pt 1):20–29.

Heiss WD, Sobesky J, Hesselmann V. Identifying thresholds for penumbra and irreversible tissue damage. Stroke 2004;35(11 suppl 1):2671–2674.

Hjort N, Butcher K, Davis SM, et al. Magnetic resonance imaging criteria for thrombolysis in acute cerebral infarct. Stroke 2005;36(2):388–397.

Hossmann KA. Periinfarct depolarizations. Cerebrovasc Brain Metab Rev 1996;8(3):195–208.

Hossmann KA. Pathophysiology and therapy of experimental stroke. Cell Mol Neurobiol 2006;26(7-8):1057–1083.

Iadecola C, Zhang F, Casey R, et al. Delayed reduction of ischemic brain injury and neurological deficits in mice lacking the inducible nitric oxide synthase gene. J Neurosci 1997;17(23):9157–9164.

Jennett WB, Harper AM, Gillespie FC. Measurement of regional cerebral blood-flow during carotid ligation. Lancet 1966;2(7474):1162–1163.

Jones TH, Morawetz RB, Crowell RM, et al. Thresholds of focal cerebral ischemia in awake monkeys. J Neurosurg 1981;54(6):773–782.

Jovin TG, Yonas H, Gebel JM, et al. The cortical ischemic core and not the consistently present penumbra is a determinant of clinical outcome in acute middle cerebral artery occlusion. Stroke 2003;34(10):2426–2433.

Kaufmann AM, Firlik AD, Fukui MB, et al. Ischemic core and penumbra in human stroke. Stroke 1999;30(1):93–99.

Kidwell CS, Alger JR, Di Salle F, et al. Diffusion MRI in patients with transient ischemic attacks. Stroke 1999;30(6):1174–1180.

Klijn CJ, Kappelle LJ, Tulleken CA, van Gijn J. Symptomatic carotid artery occlusion: a reappraisal of hemodynamic factors. Stroke 1997;28(10):2084–2093.

Kolominsky-Rabas PL, Weber M, Gefeller O, et al. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. Stroke 2001;32(12):2735–2740.

Kristian T, Siesjo BK. Calcium in ischemic cell death. Stroke 1998;29(3):705–718.

Larrue V, von Kummer R, del Zoppo G, Bluhmki E. Hemorrhagic transformation in acute ischemic stroke. Potential contributing factors in the European Cooperative Acute Stroke Study. Stroke 1997;28(5):957–960.

Lindsberg PJ, Hallenbeck JM, Feuerstein G. Platelet-activating factor in stroke and brain injury. Ann Neurol 1991;30(2):117–129.

Lo EH. Experimental models, neurovascular mechanisms and translational issues in stroke research. Br J Pharmacol 2008;153(suppl 1):396–405.

Lo EH, Moskowitz MA, Jacobs TP. Exciting, radical, suicidal: how brain cells die after stroke. Stroke 2005;36(2):189–192.

Lyden PD, Zivin JA. Hemorrhagic transformation after cerebral ischemia: mechanisms and incidence. Cerebrovasc Brain Metab Rev 1993;5(1):1–16.

Marchal G, Beaudouin V, Rioux P, et al. Prolonged persistence of substantial volumes of potentially viable brain tissue after stroke: a correlative PET-CT study with voxel-based data analysis. Stroke 1996;27(4):599–606.

Marchal G, Benali K, Iglesias S, et al. Voxel-based mapping of irreversible ischaemic damage with PET in acute stroke. Brain 1999;122(pt 12):2387–2400.

Marcoux FW, Morawetz RB, Crowell RM, et al. Differential regional vulnerability in transient focal cerebral ischemia. Stroke 1982;13(3):339–346.

Martin RL, Lloyd HG, Cowan AI. The early events of oxygen and glucose deprivation: setting the scene for neuronal death? Trends Neurosci 1994;17(6):251–257.

Mayer TE, Schulte-Altedorneburg G, Droste DW, Brückmann H. Serial CT and MRI of ischaemic cerebral infarcts: frequency and clinical impact of haemorrhagic transformation. Neuroradiology 2000;42(4):233–239.

Mergenthaler P, Dirnagl U, Meisel A. Pathophysiology of stroke: lessons from animal models. Metab Brain Dis 2004;19(3–4):151–167.

Miyashita T, Krajewski S, Krajewska M, et al. Tumor suppressor p53 is a regulator of bcl-2 and bax gene expression in vitro and in vivo. Oncogene 1994;9(6):1799–1805.

Mohr JP. Lacunes. Stroke 1982;13(1):3–11.

Ogasawara K, Ogawa A, Doi M, et al. Prediction of acute embolic stroke outcome after local intraarterial thrombolysis: value of pretreatment and posttreatment 99mTc-ethyl cysteinate dimer single photon emission computed tomography. J Cereb Blood Flow Metab 2000;20(11):1579–1586.

Ovbiagele B, Kidwell CS, Saver JL, et al. Epidemiological impact in the United States of a tissue-based definition of transient ischemic attack. Stroke 2003;34(4):919–924.

Petty GW, Brown RD Jr, Whisnant JP, et al. Ischemic stroke subtypes: a population-based study of functional outcome, survival, and recurrence. Stroke 2000;31(5):1062–1068.

Raichle ME. The pathophysiology of brain ischemia and infarction. Clin Neurosurg 1982;29:379–389.

Read SJ, Hirano T, Abbott DF, et al. The fate of hypoxic tissue on 18F-fluoromisonidazole positron emission tomography after ischemic stroke. Ann Neurol 2000;48(2):228–235.

Ritter LS, Orozco JA, Coull BM, et al. Leukocyte accumulation and hemodynamic changes in the cerebral microcirculation during early reperfusion after stroke. Stroke 2000;31(5):1153–1161.

Rordorf G, Koroshetz WJ, Copen WA, et al. Regional ischemia and ischemic injury in patients with acute middle cerebral artery stroke as defined by early diffusion-weighted and perfusion-weighted MRI. Stroke 1998;29(5):939–943.

Rothwell NJ. Cytokines and acute neurodegeneration. Mol Psychiatry 1997;2(2):120–121.

Sacco RL, Kargman DE, Gu Q, Zamanillo MC. Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. The Northern Manhattan Stroke Study. Stroke 1995;26(1):14–20.

Schellinger PD, Fiebach JB, Jansen O, et al. Stroke magnetic resonance imaging within 6 hours after onset of hyperacute cerebral ischemia. Ann Neurol 2001;49(4):460–469.

Schlaug G, Benfield A, Baird AE, et al. The ischemic penumbra: operationally defined by diffusion and perfusion MRI. Neurology 1999;53(7):1528–1537.

Sobesky J, Zaro Weber O, Lehnhardt FG, et al. Does the mismatch match the penumbra? Magnetic resonance imaging and positron emission tomography in early ischemic stroke. Stroke 2005;36(5):980–985.

Staroselskaya IA, Chaves C, Silver B, et al. Relationship between magnetic resonance arterial patency and perfusion-diffusion mismatch in acute ischemic stroke and its potential clinical use. Arch Neurol 2001;58(7):1069–1074.

Sundt TM Jr, Sharbrough FW, Anderson RE, Michenfelder JD, et al. Cerebral blood flow measurements and electroencephalograms during carotid endarterectomy. J Neurosurg 1974;41(3):310–320.

Symon L, Branston NM, Strong AJ, Hope TD. The concepts of thresholds of ischaemia in relation to brain structure and function. J Clin Pathol Suppl (R Coll Pathol) 1977;11:149–154.

Thompson CB. Apoptosis in the pathogenesis and treatment of disease. Science 1995; 267(5203):1456–1462.

Trojaborg W, Boysen G. Relation between EEG, regional cerebral blood flow and internal carotid artery pressure during carotid endarterectomy. Electroencephalogr Clin Neurophysiol 1973;34(1):61–69.

Tyson RL, Sutherland GR, Peeling J. 23Na nuclear magnetic resonance spectral changes during and after forebrain ischemia in hypoglycemic, normoglycemic, and hyperglycemic rats. Stroke 1996;27(5):957–964.

Ueda T, Sakaki S, Yuh WT, et al. Outcome in acute stroke with successful intra-arterial thrombolysis and predictive value of initial single-photon emission-computed tomography. J Cereb Blood Flow Metab 1999;19(1):99–108.

Vaux DL, Haecker G, Strasser A. An evolutionary perspective on apoptosis. Cell 1994;76(5):777–779.

Zhang Z, Chopp M, Goussev A, Powers C. Cerebral vessels express interleukin 1beta after focal cerebral ischemia. Brain Res 1998;784(1–2):210–217.

INTRAVENOUS THROMBOLYTIC THERAPY FOR ACUTE ISCHEMIC STROKE

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ABSTRACT

Despite the emergence of many promising therapies for use in acute ischemic stroke, IV recombinant tissue-type plasminogen activator (rt-PA) within 3 hours of stroke onset is currently the only available therapy proven to lead to better patient outcomes. Rapid thrombolytic therapy can substantially limit brain injury, and early rehabilitation can improve recovery after acute ischemic stroke. This chapter emphasizes the mechanics of emergent evaluation and administration of IV rt-PA. Acute rehabilitative interventions are also outlined.

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Note: Text referenced in the Quintessentials Preferred Responses, which appear later in this issue, is indicated in yellow shading throughout this chapter.

INTRODUCTION

In 1996, recombinant tissue-type plasminogen activator (rt-PA) (alteplase) was approved by the US Food and Drug Administration (USFDA) for acute ischemic stroke within 3 hours of symptom onset, based on two randomized phase 3 trials jointly published as the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study (Class A Evidence) (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995).

Promising therapies have since emerged. In 1999, intraarterial delivery of recombinant prourokinase for acute middle cerebral artery occlusions within 6 hours of symptom onset was shown to be effective in one phase 3 trial (Furlan et al, 1999). The USFDA required two phase 3 trials for approval of this drug. A second trial was never done, and the drug is no longer available. Based on this trial, however, intraarterial therapy with rt-PA has become an option for patients who have major middle cerebral artery strokes and who are ineligible for other therapy (Adams et al, 2007). In 2005, intraarterial mechanical clot retrieval with

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the Merci Retriever® device was USFDA approved as an effective device for extracting clot in the intracranial vasculature based on a single-arm phase 2 trial (Smith et al, 2005). Additional evidence is needed to show that this treatment approach improves clinical outcome in randomized trials, and two phase 3 trials using this device are underway. These, and additional promising approaches to acute stroke treatment, are discussed further in the chapter ''Emerging Therapies.''

IV thrombolytic therapy remains the cornerstone of evidence-based acute ischemic stroke therapy. Unfortunately, despite the approval of thrombolytic therapy since 1996, the use of IV rt-PA has been limited to 2% to 8.5% of patients with acute ischemic stroke based on population-based data from 2004 (Arora et al, 2005; Bambauer et al, 2006; Kleindorfer et al, 2003). A commonly cited reason is delayed presentation to emergency departments (Kleindorfer et al, 2004). Additionally, improved organization at the hospital level, including the implementation of stroke teams, has been well documented to increase rates of rt-PA use in many communities. Programs to develop better health care infrastructural support for delivery of acute stroke interventions are underway (see the chapter ''Primary Stroke Center Certification'') (Schwamm et al, 2005). Hospital reimbursement for acute IV thrombolysis has also been increased as of October 2005 (Demaerschalk and Durocher, 2007). These approaches may increase acute stroke treatment rates in the future.

Up to 50% of patients never gain functional independence after ischemic stroke (Rosamond et al, 2007). Interventions aimed at recovery of function are therefore critical. This chapter will briefly outline the current clinical practice guidelines regarding acute rehabilitation interventions.

REPERFUSION THERAPY

IV rt-PA is efficacious and cost-effective for patients with acute ischemic stroke treated within 3 hours of symptom onset (Demaerschalk and Yip, 2005; The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995). In part 2 of the NINDS trial, 39% of rt-PA cases and 26% of placebo cases achieved minimal or no disability based on a modified Rankin score of 0 to 1. (Similar results were seen in a 3-month analysis of part 1 of the trial.) This translates to a number needed to treat of eight for one additional patient to achieve minimal or no disability. This number accounts for the 6.6% of patients who suffer the severe complication of symptomatic intracranial hemorrhage (sICH). Furthermore, it has been suggested that the number needed to treat to contribute to *any* improvement in clinical outcome may be as a low as three (Saver, 2004).

The findings of the NINDS trial are robust. Benefit of IV rt-PA was seen among all subgroups and in multiple reanalyses using alternate end points (Ingall et al, 2004; Johnston et al, 2004; Kwiatkowski et al, 2005; Marler et al, 2000; Optimising Analysis of Stroke Trials (OAST) Collaboration et al, 2007; Saver and Yafeh, 2007). Similar results have been seen in community cohorts that follow the NINDS rt-PA protocol (Graham, 2003).

Emergency Department Evaluation

Faster administration of IV rt-PA is associated with better clinical outcomes (Hacke et al, 2004; Marler et al, 2000), underscoring an emphasis on minimizing door-to-needle times in the emergency department, as demonstrated by **Case 3-1**. A guide for maximum times for emergent evaluation steps and treatment of acute

KEY POINTS

- IV recombinant tissue-type plasminogen activator (rt-PA) is efficacious and cost-effective for patients with acute ischemic stroke treated within 3 hours of symptom onset.
- The number needed to treat for one additional patient to achieve minimal or no disability is eight.
- Faster administration of IV rt-PA is associated with better clinical outcomes, underscoring an emphasis on minimizing door-to-needle times in the emergency department.

Case 3-1

A 45-year-old woman was at a grocery store with her daughter when she suddenly slumped over and became nonverbal at 4:05 PM. Her daughter called 911 immediately. The patient arrived at the emergency department at 4:20 PM and was immediately noted to have global aphasia and severe right hemiparesis. The emergency physician called the stroke team at 4:30 PM while the patient was taken for CT imaging.

Upon the stroke physician's arrival at 4:50 PM, a CT scan had been performed. No intracranial hemorrhage or clear hypodensity was seen. While reviewing further eligibility for administration of IV rt-PA, the stroke physician asked the stroke team nurse to begin mixing the rt-PA (1:1 dilution), which was stored in the emergency department medication-dispensing system. The time that the patient was last seen normal was confirmed. Blood pressure was 160/85 mm Hg. The general medical examination was unremarkable. National Institutes of Health Stroke Scale (NIHSS) score was 18. Finger-stick blood sugar level was 114 mg/dL. EKG showed normal sinus rhythm and no ST changes. Complete blood count and coagulation results had not been returned at this time, but it was verified by her daughter that the patient's medications did not include warfarin or heparin and her medical history was unremarkable. The risks and benefits of rt-PA were discussed with the daughter, and rt-PA was recommended. Treatment was initiated at 5:15 PM. Specifically, an IV rt-PA bolus (10% of 0.9 mg/kg with maximum dose of 90 mg) followed by infusion (remaining 90% over 60 minutes) was initiated at 70 minutes from stroke onset. During the infusion, the patient made a dramatic recovery, and at 24 hours, she was fluent with only a mild right hemiparesis (NIHSS score of 3).

Comment. Rapid emergency medical services activation, prompt triage, early stroke team activation prior to the head CT, prompt eligibility evaluation, and concurrent preparation of rt-PA stored in the emergency department allowed this patient to be treated in 2 hours. Every effort should be made to streamline this process for efficiency, as faster initiation of rt-PA treatment leads to a greater likelihood of a good clinical outcome (**Figure 3-1**).

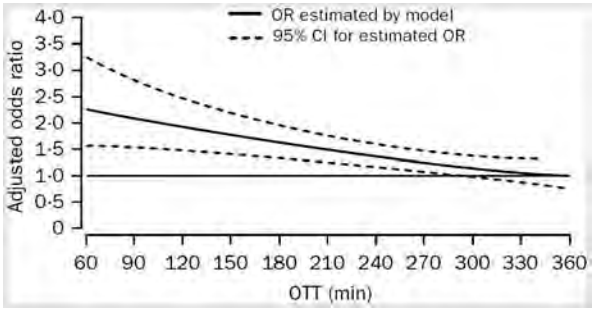

FIGURE 3-1 The above figure demonstrates that the likelihood of a favorable clinical outcome diminishes as time to the initiation of IV rt-PA initiation increases. This model was derived from a pooled analysis of major IV rt-PA strokes trials—the ATLANTIS Parts A and B, ECASS I and II, and National Institute of Neurological Disorders and Stroke Parts I and II trials—after adjustment for age, baseline glucose concentration, baseline National Institutes of Health Stroke Scale (NIHSS) score, baseline diastolic blood pressure, history of hypertension, and interaction between age and baseline NIHSS measurement. The likelihood of a favorable clinical outcome was determined by estimating odds ratios for 90-day NIHSS 0 to 1, modified Rankin Scale 0 to 1, and Barthel Index 95 to 100, using a global statistical approach.

CI = confidence interval; OR = odds ratio; OTT = overall treatment time; rt-PA = recombinant tissue-type plasminogen activator.

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TABLE 3-1 **National Institute of Neurological Disorders and Stroke-Recommended Time Frames for Recombinant Tissue-Type Plasminogen Activator Evaluation and Treatment**

Time From Emergency Department Arrival	Action
10 minutes	Evaluate potential stroke patient (emergency department physician)
15 minutes	Notify stroke team or physician with stroke expertise
25 minutes	Initiate head CT
45 minutes	Interpret head CT
60 minutes	Administer IV recombinant tissue-type plasminogen activator (ie, door-to-needle time)

ischemic stroke was established by the 1997 NINDS National Symposium on Rapid Identification and Treatment of Stroke (Marler et al, 1997) as shown in **Table 3-1**.

After establishing cardiopulmonary stability, the emergent stroke evaluation includes the following key steps:

- Establish time of stroke onset based on the time the patient was

Case 3-2

A 98-year-old woman with a history of hypertension presented to the emergency department after her husband found her with acute left hemiplegia while watching television. Emergency department staff called the stroke team at 11:50 PM and reported a head CT with no intracranial hemorrhage at 2 hours from symptom onset.

The stroke physician arrived at 12:15 AM. The general examination was notable for an irregularly irregular heart rate of 120. The NIHSS score was 13. Complete blood count, chemistry, and coagulation laboratory results were unremarkable. EKG showed atrial fibrillation. The husband confirmed no recent surgeries, bleeding issues, or history of intracranial hemorrhage. The stroke physician requested that rt-PA be mixed while reviewing the CT scan. The CT scan showed no intracranial hemorrhage but also showed clear hypodensity (darker than white matter) in the left basal ganglia region. Based on this finding, he deemed the patient ineligible for rt-PA and asked for the rt-PA to be discarded; the cost of the drug was reimbursed to the hospital. Upon further questioning, the patient's husband noted that he found her in the bedroom watching television and with left-sided weakness at 9:50 PM. He had last seen her in a normal neurologic state at 7:00 PM when they had completed eating dinner.

Comment. This case exemplifies the importance of seeking not the time of stroke onset, but the ''time last seen normal.'' It is a common source of error, and treatment at later time points is likely to risk intracranial hemorrhage without benefit. This sometimes takes creative questioning, including calling neighbors, checking cell phone call histories, checking television guides for times of programs watched, and other clues for a time last seen normal.

last seen in a usual state of health, as is demonstrated by **Case 3-2**.

- Obtain further historical data to help exclude alternative diagnoses (stroke mimics) and to rule out contraindications to rt-PA administration.
- Calculate the NIHSS score (see **Table 1-3** in the chapter "Diagnosis of Stroke and Stroke Mimics in the Emergency Setting").
- Perform diagnostic studies, particularly head CT, to rule out intracranial hemorrhage (**Table 3-2**).

Eligibility

Standard eligibility criteria are based on the precedent set by the NINDS trial and have since been revised and published in guidelines by the American Heart Association (AHA) (**Table 3-3**).

Notes on specific eligibility criteria are:

- Acute ischemic stroke is typically a clinical diagnosis. A noncontrast CT scan is necessary to exclude intracranial hemorrhage. When the diagnosis is unclear, additional neuroimaging studies, such as MRI or CT angiography, may be helpful (Adams et al, 2007).
- Minor or isolated symptoms typically are not treated. However, treating isolated disabling symptoms, such as aphasia, is reasonable.
- If the exact time of symptom onset cannot be determined, then the time the patient was last seen to be normal should be substituted for the time of symptom onset. For example, if the patient woke up with new symptoms, then the time the patient went to bed is used as the time of onset.
- The finger-stick blood glucose level should be reviewed during the eligibility evaluation since this

TABLE 3-2 Diagnostic Studies to Be Performed in the Emergency Department Setting

- ▶ Noncontrast head CT (or MRI if it will not delay treatment)
- ▶ Finger-stick blood glucose
- ▶ Serum electrolytes/renal function tests
- ▶ EKG
- ▶ Cardiac enzymes
- ▶ Complete blood count, including platelet count[a]
- ▶ International normalized ratio[a]
- ▶ Activated partial thromboplastin time[a]
- ▶ Oxygen saturation

[a]Unless suspicion for abnormalities in these values exists, therapy should not be delayed while awaiting these results.

Adapted with permission from Adams HP Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists [published errata appears in Stroke 2007;38(6):e38 and Stroke 2007;38(9):e96]. Stroke 2007;38(6):1655–1711.

TABLE 3-3 Eligibility Criteria for Recombinant Tissue-Type Plasminogen Activator Therapy

- Diagnosis of ischemic stroke causing measurable neurologic deficit
- Neurologic signs not clearing spontaneously
- Neurologic signs not minor and isolated
- Caution exercised in treating a patient with major deficits
- Symptoms of stroke not suggestive of subarachnoid hemorrhage
- Onset of symptoms less than 3 hours before beginning treatment
- No head trauma or prior stroke in the previous 3 months
- No myocardial infarction in the previous 3 months
- No gastrointestinal or urinary tract hemorrhage in the previous 21 days
- No major surgery in the previous 14 days
- No arterial puncture at a noncompressible site in the previous 7 days
- No history of previous intracranial hemorrhage
- Blood pressure not elevated (systolic $\geq$185 mm Hg and diastolic $\geq$110 mm Hg)
- No evidence of active bleeding or acute trauma (fracture) on examination
- Patient not taking an oral anticoagulant or, if anticoagulant being taken, international normalized ratio $\leq$1.7
- If patient has received heparin in the previous 48 hours, a partial prothrombin time in the normal range
- Platelet count not $\leq$100,000 mm^3
- Blood glucose concentration not $\leq$50 mg/dL (2.5 mmol/L)
- No seizure with postictal residual neurologic impairments
- CT showing no multilobar infarction (hypodensity greater than one-third cerebral hemisphere)
- Patient or family members understanding of the potential risks and benefits of treatment

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can always be obtained rapidly. It is reasonable to proceed with IV rt-PA administration prior to obtaining coagulation and platelet results if there is no clinical suspicion of a potential abnormality and awaiting theses results would delay treatment. (Cucchiara et al, 2007; Gottesman et al, 2006).

- Treatment in the setting of myocardial infarction is often a consideration in consultation with cardiology. If symptoms or signs of pericarditis are present, however, then a risk of hemopericardium is also present (Kasner et al, 1998).
- Stroke patients with recent surgery may be considered for intraarterial

therapy based on retrospective studies (Adams et al, 2007; Chalela et al, 2001; Katzan et al, 1999).

- Attempts at lowering blood pressure may be undertaken to obtain the required parameter of less than 185/110 mm Hg. However, only nonaggressive measures may be used because of concerns for o therwise higher risks of intracranial hemorrhage with rt-PA therapy. No evidence-based guidelines for "nonaggressive measures" are currently available. The AHA recommendations are presented as one potential guide (**Table 3-4**).

TABLE 3-4 Approach to Hypertension in Acute Ischemic Stroke

▶ **If Patient Is Eligible for Treatment With IV Recombinant Tissue-Type Plasminogen Activator**

Blood pressure level of systolic greater than 185 mm Hg or diastolic greater than 110 mm Hg

Labetalol 10 mg IV to 20 mg IV over 1 to 2 minutes; may repeat once

Or nitropaste 1 to 2 inches

Or nicardipine infusion, 5 mg/h, titrate up by 2.5 mg/h at 5- to 15-minute intervals, maximum dose 15 mg/h; when desired blood pressure is attained, reduce to 3 mg/h

If blood pressure does not decline and remains greater than 185/110 mm Hg, do not administer rt-PA

▶ **Management of Blood Pressure During and After Treatment With Recombinant Tissue-Type Plasminogen Activator or Other Acute Reperfusion Intervention**

Monitor blood pressure every 15 minutes during treatment and then for another 2 hours; then every 30 minutes for 6 hours; and then every hour for 16 hours

Blood pressure level

Systolic 180 mm Hg to 230 mm Hg or diastolic 105 mm Hg to 120 mm Hg

Labetalol 10 mg IV over 1 to 2 minutes; may repeat every 10 to 20 minutes, maximum dose of 300 mg

Or labetalol 10 mg IV followed by an infusion at 2 mg/min to 8 mg/min

Systolic greater than 230 mm Hg or diastolic 121 mm Hg to 140 mm Hg

Labetalol 10 mg IV over 1 to 2 minutes; may repeat every 10 to 20 minutes, maximum dose of 300 mg

Or labetalol 10 mg IV followed by an infusion at 2 mg/min to 8 mg/min

Or nicardipine infusion, 5 mg/h, titrate up to desired effect by increasing 2.5 mg/h every 5 minutes to maximum of 15 mg/h

If blood pressure is not controlled, consider sodium nitroprusside

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- On occasion, patients present with a seizure at the time of symptom onset. In this case, treatment with rt-PA may be warranted if there is a confirmed ischemic stroke (for example by MRI or CT angiography) and the neurologic deficits are largely attributed to the stroke and not to a Todd (postictal) phenomenon (Adams et al, 2007).
- When considering hypodensity on head CT, subtle changes should not be used for exclusion based on current evidence. Changes should be clear (darker than white matter and brighter than CSF) in a large area (such as greater than one-third middle cerebral artery territory) (Khatri et al, 2007).
- Consent is not required for IV rt-PA as it is considered the standard of care. However, discussion with the patient and/or family is important if possible.

Administration

The only USFDA-approved thrombolytic medication for acute ischemic stroke is rt-PA (alteplase). This should not be confused with r-PA (reteplase) or TNK (tenecteplase), for example, which are available for coronary artery reperfusion and under clinical investigation for stroke treatment.

Rapid access to the drug is recommended. Preferably rt-PA should be stored in the emergency department. The drug is mixed in a 1:1 dilution with provided sterile water (normal saline is acceptable as well) with gentle swirling, but not shaking.

Dosing for acute ischemic stroke is 0.9 mg/kg (maximum of 90 mg). Ten percent is administered as a bolus over 1 to 2 minutes, and the remainder is administered as a continuous infusion over 60 minutes. It should be noted that this is lower than the myocardial infarction dose of 1.1 mg/kg, as there is concern that the risk of symptomatic intracranial hemorrhage would be unacceptably high with the cardiac dose based on pilot trials (Khatri et al, 2007).

Patient Monitoring During/After Treatment

Preventing and identifying sICH are the foci of patient management both during the rt-PA infusion and in the first 24 hours after administration.

Frequent monitoring of vital signs and clinical and neurologic status is recommended. Typically, the patient is assessed every 15 minutes during the rt-PA infusion, every 30 minutes for the next 7 hours, and every hour for the next 16 hours.

Blood pressure greater than 180/105 mm Hg should prompt urgent treatment (**Table 3-4**). In contrast to the time period prior to initiation of rt-PA, treatment of hypertension after rt-PA should be aggressive.

Changes in clinical status of particular concern are worsening of the neurologic deficit, a new neurologic deficit, new or worsening headache, or nausea/vomiting. These symptoms should lead to prompt discontinuation of rt-PA (if still infusing) and emergent CT scan to rule out sICH. If there is no sICH, the rt-PA infusion may be reinitiated and efforts to provide symptomatic relief are appropriate. Management of sICH is discussed further below. Rarely, as discussed below, angioedema may be observed during monitoring.

Management of Symptomatic Intracranial Hemorrhage Associated With Recombinant Tissue-Type Plasminogen Activator Use

sICH, the most feared complication of rt-PA therapy, is associated with a

KEY POINTS

- Preventing and identifying symptomatic intracranial hemorrhage are the foci of patient management both during the rt-PA infusion and in the first 24 hours after administration.
- In contrast to recommended management during the time period prior to initiation of rt-PA, treatment of hypertension after rt-PA should be aggressive.
- Symptomatic intracranial hemorrhage, the most feared complication of rt-PA therapy, is associated with a 45% mortality rate.

KEY POINT

- Angioedema is typically seen in 1% to 2% of patients treated with rt-PA and may occur in as many as 5.1% of patients if detailed examinations are performed.

45% mortality rate (National Institute of Neurological Disorders and Stroke, 1995). Current treatment recommendations include urgent transfusion of platelets (6 units to 8 units) and cryoprecipitate (6 units to 8 units). No reliable data are available regarding the optimal approach. The NINDS trial protocol with updates for current medical practice is provided as a guide (**Figure 3-2**).

Management of Angioedema Associated With Recombinant Tissue-Type Plasminogen Activator Use

Angioedema is typically seen in 1% to 2% of patients treated with rt-PA and may be seen in as many as 5.1% of patients if detailed examinations are performed. It is more common in patients on angiotensin-converting enzyme inhibitors and in patients with frontal and insular ischemic infarcts. When orolingual swelling is unilateral, it is most often on the contralateral side. While the course is typically benign, vigilant monitoring and treatment are recommended (Hill et al, 2003; Pancioli et al, 1997). While there is no evidence for a specific treatment protocol, a suggested protocol used at the University of Cincinnati is shown in **Figure 3-3**.

IV rt-PA BEYOND 3 HOURS: AN UPDATE FROM THE ECASS III TRIAL

The results of the third European Cooperative Acute Stroke Study (ECASS III) were published in September 2008 (Hacke et al, 2008). The study was conceived after a pooled analysis of previous major IV rt-PA trials had suggested a beneficial effect, albeit smaller, of IV rt-PA when given more than 3 hours after symptom onset as shown in **Figure 3-1** (Hacke et al, 2004).

ECASS III was designed to test the hypothesis that IV rt-PA would be effective when administered between 3 and 4.5 hours after onset of symptoms in patients with acute ischemic stroke. Patients were randomized in a double-blind fashion to receive either 0.9 mg/kg of rt-PA (n = 418) or placebo (n = 403). Disability at 90 days was assessed by the modified Rankin Scale and dichotomized as a favorable outcome (score of 0 or 1) or an unfavorable clinical outcome (score of 2 to 6). Intracranial hemorrhage associated with clinical deterioration (greater than a 4-point increase in NIHSS score) or death was considered symptomatic in ECASS III.

Compared with the NINDS rt-PA trial (National Institute of Neurological Disorders and Stroke rt-PA Stroke Study, 1995), the design of ECASS III had three notable differences in exclusion criteria:

(1) Exclusion criteria included age greater than 80 years
(2) Severe stroke (NIHSS score greater than 25)
(3) History of diabetes with prior stroke

Treatment with rt-PA was significantly associated with a favorable outcome at 3 months (odds ratio, 1.34; 95% confidence interval, 1.02 to 1.76). Compared to placebo, the absolute increase in favorable outcome for the treatment group was 7.2% (52.4% versus 45.2%, $P = .04$), suggesting a number needed to treat of 14. Symptomatic intracranial hemorrhage was significantly more frequent in the treatment group (2.4% versus 0.2%, $P = .008$). Mortality was similar for both groups, with a nonsignificant trend favoring the rt-PA group (7.7% versus 8.4%, $P = .68$). The authors concluded

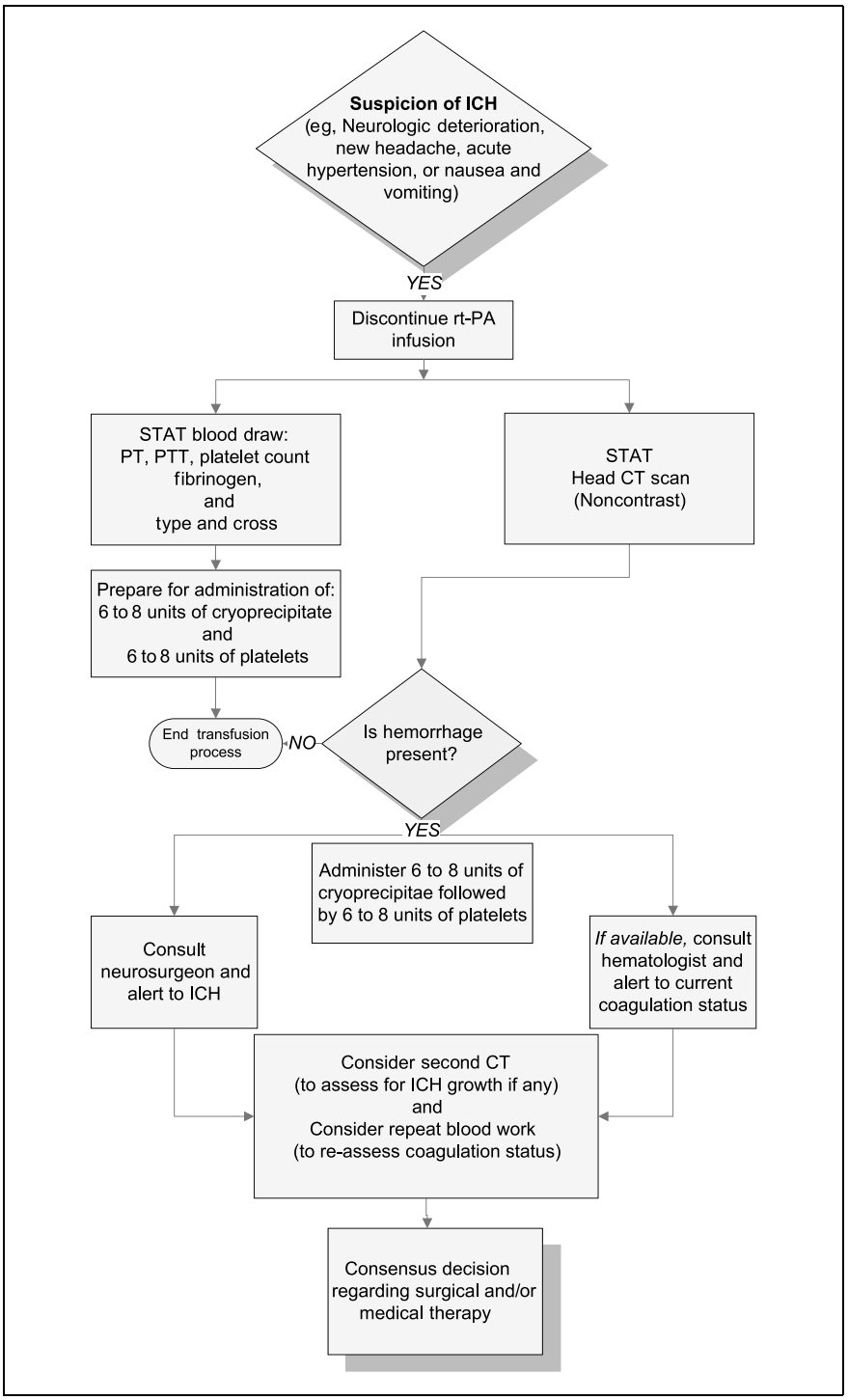

FIGURE 3-2 Modified National Institute of Neurological Disorders and Stroke management protocol for intracranial hemorrhage.

ICH = intracranial hemorrhage; rt-PA = recombinant tissue-type plasminogen activator; STAT = at once; PT = prothrombin time; PTT = partial thromboplastin time.

Modified from National Institute of Neurological Disorders and Stroke.

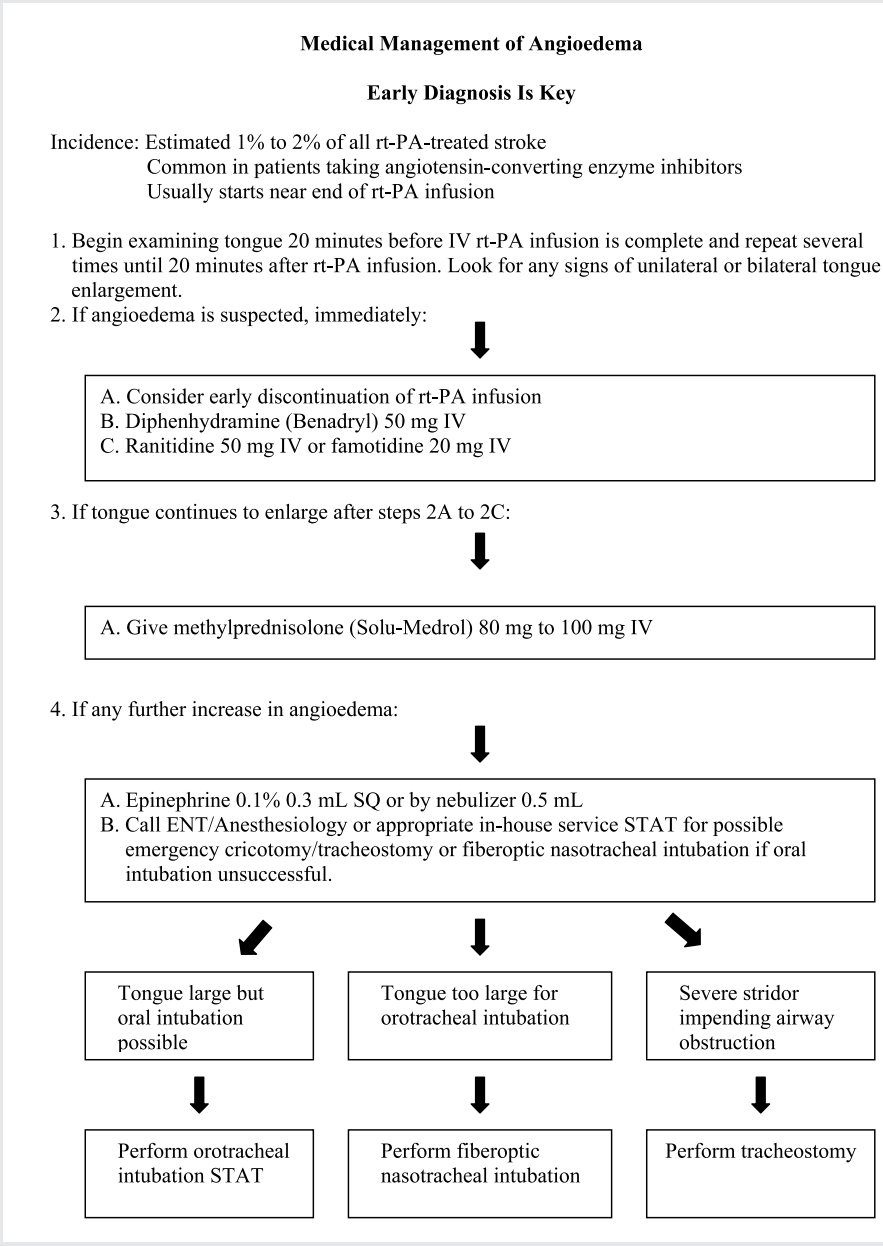

FIGURE 3-3 Medical management of angioedema after IV recombinant tissue-type plasminogen activator.

rt-PA = recombinant tissue-type plasminogen activator; SQ = subcutaneous; ENT = ears, nose, and throat; STAT = at once.

that IV rt-PA given 3 to 4.5 hours after the onset of stroke symptoms was associated with a modest but significant improvement in clinical outcomes.

The findings of the ECASS III trial confirm the safety and efficacy of IV rt-PA for acute ischemic stroke. Updated consensus statements incorporating the results of ECASS III into routine clinical practice for ischemic strokes beyond 3 hours from symptom onset are pending. The emphasis should remain on treating patients

with acute ischemic stroke as quickly as possible after symptom onset.

INTERVENTIONS FOR PATIENTS INELIGIBLE FOR RECOMBINANT TISSUE-TYPE PLASMINOGEN ACTIVATOR

Antithrombotics

While some studies suggest that acute anticoagulation may prevent recurrent stroke and may improve recanalization, numerous acute stroke trials suggest that the risk of intracranial hemorrhage associated with systemic anticoagulation outweighs any benefit. (Bath et al, 2001; Berge et al, 2000; International Stroke Trial Collaborative Group, 1997; Publications Committee for the trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators, 1998). There are insufficient data to recommend its use in subgroups such as those with large artery stenosis or cardiac thrombus (Adams et al, 2007). In addition, the use of anticoagulation in the hyperacute setting (less than 3 hours) requires further study (Camerlingo et al, 2005).

Initiation of antiplatelet therapy within 48 hours of ischemic stroke has been shown to be effective at preventing recurrent stroke with an absolute benefit of about 1% over the first 2 weeks poststroke (CAST [Chinese Acute Stroke Trial] Collaborative Group, 1997). However, antiplatelet therapy has no demonstrated role in improving outcome from the incident ischemic stroke. Additional acute prevention strategies are discussed in the chapter ''Primary Stroke Center Certification.''

ACUTE REHABILITATION INTERVENTIONS

Acute stroke is the leading cause of disability in the United States (Centers for Disease Control and Prevention [CDC], 2005). Maximizing functional recovery after an ischemic stroke is an important goal.

Based on the AHA-endorsed Veterans Affairs/Department of Defense clinical practice guideline (Duncan et al, 2005), the following rehabilitation interventions are strongly recommended:

- Organized and coordinated postacute inpatient care
- Early initiation of rehabilitation therapy
- Long-term evaluation and treatment by stroke language pathologists
- Use of training to improve attention in the poststroke setting
- Pharmacotherapy for depression and emotional lability

Additional specific interventions that may be beneficial include acute speech therapy, partial body weight–supported treadmill training, functional electrical stimulation, pharmacologic treatment of spasticity, treatments focusing on functional adaptation for visual and spatial neglect, and the use of pharmaceutical agents (such as dextroamphetamine and fluoxetine) believed to enhance stroke recovery.

Interventions that require further investigation include specific dysphagia treatments, neurodevelopmental training, and biofeedback.

The aforementioned clinical guidelines provide a detailed discussion of these rehabilitation interventions for the interested reader.

KEY POINTS

- While some studies suggest that acute anticoagulation may prevent recurrent stroke and may improve recanalization, numerous acute stroke trials suggest that the risk of intracranial hemorrhage associated with systemic anticoagulation outweighs any benefit.
- Initiation of antiplatelet therapy within 48 hours of ischemic stroke has been shown to be effective at preventing recurrent stroke with an absolute benefit of about 1% over the first 2 weeks poststroke.
- Acute stroke is the leading cause of disability in the United States.

KEY POINT

- The following rehabilitation interventions are strongly recommended: organized and coordinated postacute inpatient care, early initiation of rehabilitation therapy, long-term evaluation and treatment by stroke language pathologists, use of training to improve attention in the poststroke setting, and pharmacotherapy for depression and emotional lability.

REFERENCES

Adams H Jr, del Zoppo G, Alberts M, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists [published errata appear in Stroke 2007;38(6):e38 and Stroke 2007; 38(9):e96]. Stroke 2007;38(5):1655–1711.

Arora S, Broderick JP, Frankel M, et al. Acute stroke care in the US: results from 4 pilot prototypes of the Paul Coverdell National Acute Stroke Registry [published errata appears in Stroke 2005;36(8):1820]. Stroke 2005;36(6):1232–1240.

Bambauer KZ, Johnston SC, Bambauer DE, Zivin JA. Reasons why few patients with acute stroke receive tissue plasminogen activator. Arch Neurol 2006;63(5):661–664.

Bath PM, Lindenstrom E, Boysen G, et al. Tinzaparin in acute ischaemic stroke (TAIST): a randomised aspirin-controlled trial [published erratum appears in Lancet 2001; 358(9289):1276]. Lancet 2001;358(9283):702–710.

Berge E, Abdelnoor M, Nakstad PH, Sandset PM. Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: a double-blind randomised study. HAEST Study Group. Heparin in Acute Embolic Stroke Trial. Lancet 2000;355(9211):1205–1210.

Camerlingo M, Salvi P, Belloni G, et al. Intravenous heparin started within the first 3 hours after onset of symptoms as a treatment for acute nonlacunar hemispheric cerebral infarctions. Stroke 2005;36(11):2415–2420.

CAST (Chinese Acute Stroke Trial) Collaborative Group. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. Lancet 1997;349(9066):1641–1649.

Centers for Disease Control and Prevention (CDC). Differences in disability among black and white stroke survivors—United States, 2000–2001. MMWR Morb Mortal Wkly Rep 2005;54(1):3–6.

Chalela JA, Katzan I, Liebeskind DS, et al. Safety of intra-arterial thrombolysis in the postoperative period. Stroke 2001;32(6):1365–1369.

Cucchiara BL, Jackson B, Weiner M, Messe SR. Usefulness of checking platelet count before thrombolysis in acute ischemic stroke. Stroke 2007;38(5): 1639–1640.

Demaerschalk BM, Durocher DL. How diagnosis-related group 559 will change the US Medicare cost reimbursement ratio for stroke centers. Stroke 2007;38(4): 1309–1312.

Demaerschalk BM, Yip TR. Economic benefit of increasing utilization of intravenous tissue plasminogen activator for acute ischemic stroke in the United States. Stroke 2005;36(11):2500–2503.

Duncan PW, Zorowitz R, Bates B, et al. Management of adult stroke rehabilitation care: a clinical practice guideline. Stroke 2005;36(9):e100–e143.

Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in acute cerebral thromboembolism. JAMA 1999;282(21):2003–2011.

Gottesman RF, Alt J, Wityk RJ, Llinas RH. Predicting abnormal coagulation in ischemic stroke: reducing delay in rt-PA use. Neurology 2006;67(9):1665–1667.

Graham GD. Tissue plasminogen activator for acute ischemic stroke in clinical practice: a meta-analysis of safety data. Stroke 2003;34(12):2847–2850.

Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet 2004; 363(9411):768–774.

Hacke W, Kaste M, Bluhmki E, et al; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359(13):1317–1329.

Hill MD, Lye T, Moss H, et al. Hemi-orolingual angioedema and ACE inhibition after alteplase treatment of stroke. Neurology 2003;60(9):1525–1527.

Ingall TJ, O'Fallon WM, Asplund K, et al. Findings from the reanalysis of the NINDS tissue plasminogen activator for acute ischemic stroke treatment trial. Stroke 2004;35(10):2418–2424.

International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. Lancet 1997;349(9065):1569–1581.

Johnston KC, Connors AF Jr, Wagner DP, Haley EC Jr. Risk adjustment effect on stroke clinical trials. Stroke 2004;35(2):e43–e45.

Kasner SE, Villar-Cordova CE, Tong D, Grotta JC. Hemopericardium and cardiac tamponade after thrombolysis for acute ischemic stroke. Neurology 1998;50(6): 1857–1859.

Katzan IL, Masaryk TJ, Furlan AJ, et al. Intra-arterial thrombolysis for perioperative stroke after open heart surgery. Neurology 1999;52(5):1081–1084.

Khatri P, Wechsler LR, Broderick JP. Intracranial hemorrhage associated with revascularization therapies. Stroke 2007;38(2):431–440.

Kleindorfer D, Khoury J, Alwell K, et al. rt-PA use in a population-based study: the post-FDA approval era. Stroke 2003;34(1):283.

Kleindorfer D, Kissela B, Schneider A, et al. Eligibility for recombinant tissue plasminogen activator in acute ischemic stroke: a population-based study. Stroke 2004;35(2):e27–e29.

Kwiatkowski T, Libman R, Tilley BC, et al. The impact of imbalances in baseline stroke severity on outcome in the National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study. Ann Emerg Med 2005;45(4): 377–384.

Marler J, Jones P, Emr M. Rapid identification and treatment of acute stroke. Presented at: National Symposium on Rapid Identification and Treatment of Acute Stroke; August 1997.

Marler JR, Tilley BC, Lu M, et al. Early stroke treatment associated with better outcome: The NINDS rt-PA stroke study. Neurology 2000;55(11):1649–1655.

The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995; 333(24):1581–1587.

Optimising Analysis of Stroke Trials (OAST) Collaboration, Bath PM, Gray LJ, Collier T, et al. Can we improve the statistical analysis of stroke trials? Statistical reanalysis of functional outcomes in stroke trials. Stroke 2007;38(6):1911–1915.

Pancioli A, Brott T, Donaldson V, Miller R. Asymmetric angioneurotic edema associated with thrombolysis for acute stroke. Ann Emerg Med 1997;30(2):227–229.

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(16):1265–1272.

Rosamond W, Flegal K, Friday G, et al. Heart disease and stroke statistics–2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee [published errata appears in Circulation 2007,115(5):e172]. Circulation 2007;115(5):e69–e171.

Saver JL. Number needed to treat estimates incorporating effects over the entire range of clinical outcomes: novel derivation method and application to thrombolytic therapy for acute stroke [published errata appears in Arch Neurol 2004;61(10):1599]. Arch Neurol 2004;61(7):1066–1070.

Saver JL, Yafeh B. Confirmation of tPA treatment effect by baseline severity-adjusted end point reanalysis of the NINDS-tPA stroke trials. Stroke 2007;38(2):414–416.

Schwamm LH, Pancioli A, Acker JE 3rd, et al; American Stroke Association's Task Force on the Development of Stroke Systems. Recommendations for the establishment of stroke systems of care: recommendations from the American Stroke Association's Task Force on the Development of Stroke Systems. Stroke 2005;36(3):690–703.

Smith WS, Sung G, Starkman S, et al. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: Results of the MERCI trial. Stroke 2005;36(7):1432–1438.

COMPLICATIONS OF ISCHEMIC STROKE: PREVENTION AND MANAGEMENT

Kevin M. Barrett, Pooja Khatri, Tudor G. Jovin

ABSTRACT

Prevention and proper management of complications in the hospitalized patient with stroke may improve both short-term and long-term prognosis. General medical and neurologic complications may be encountered in the early days after stroke. Common medical complications include deep venous thrombosis, pulmonary embolism, falls, systemic infections, and neuropsychiatric disturbances. Frequent neurologic complications include cerebral edema, elevated intracranial pressure, hemorrhagic transformation, and seizures. Anticipation of complications can expedite initiation of preventive and therapeutic measures. This chapter focuses on common medical and neurologic complications that occur after stroke in the acute hospital setting.

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Note: Text referenced in the Quintessentials Preferred Responses, which appear later in this issue, is indicated in yellow shading throughout this chapter.

KEY POINTS

- Medical complications after stroke are frequent and have been reported in up to 85% of hospitalized patients with stroke.
- Medical complications negatively impact short-term functional outcomes and mortality.

PREVENTION AND TREATMENT OF ACUTE MEDICAL COMPLICATIONS

Medical complications after stroke are frequent and have been reported in up to 85% of hospitalized patients with stroke (Langhorne et al, 2000) and negatively impact short-term functional outcomes and mortality (Johnston et al, 1998). **Table 4-1** lists common post-stroke medical complications. The negative impact of in-hospital complications on mortality can be measured as far out as 4 years poststroke (Bae et al, 2005). Complications related to immobility and infection are most commonly encountered by the clinician caring for hospitalized patients with stroke.

Deep Venous Thrombosis and Pulmonary Embolism

Lower extremity deep venous thrombosis (DVT) may occur in up to half of patients with hemiplegic stroke without the use of heparin prophylaxis (Kelly et al, 2001). The highest incidence occurs between the second and seventh day poststroke. Elderly patients and those immobilized after stroke appear to be at highest risk (Kelly et al, 2004b). Dehydration, long assumed to predispose to DVT, was independently

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TABLE 4-1 Medical Complications in Hospitalized Patients With Stroke

▶ **Complications of Immobility**
Deep vein thrombosis/pulmonary embolism
Falls
Pressure sores or ulceration
▶ **Infections**
Chest infection
Urinary tract infection
Other infections
▶ **Malnutrition**
Dysphagia
Dehydration
▶ **Pain**
Shoulder pain (subluxation in the paretic limb)
Miscellaneous pain (headache, musculoskeletal)
▶ **Neuropsychiatric Disturbances**
Depression
Acute confusional states (delirium)
▶ **Miscellaneous**
Cardiac complications (arrhythmia, myocardial ischemia)
Gastrointestinal bleed
Constipation

associated with venous thromboembolism in a cohort of patients with acute ischemic stroke (Kelly et al, 2004a). The greatest clinical concern related to proximal DVT is fatal pulmonary embolism (PE). Estimates of early deaths attributable to PE range from 13% to 25% and occur most frequently between the second and fourth week (Kelly et al, 2001). Asymptomatic DVT may cause PE, but the exact frequency and clinical significance are unknown. The postthrombotic syndrome is characterized by pain, edema, heaviness, and skin changes in the affected limb and may develop in up to 50% of patients with symptomatic DVT (Kahn, 2006). For these reasons, DVT may slow recovery and rehabilitation after stroke.

Measures to prevent DVT should be routine for all patients with ischemic stroke admitted to the hospital. Available options for DVT prophylaxis are presented in **Table 4-2**. Recommendations support early mobilization after stroke as an effective measure to reduce the likelihood of DVT and other poststroke complications. However, hemodynamically unstable patients or those with fluctuating symptoms cannot be safely mobilized. Also, patients treated with thrombolytics are routinely kept on bed rest for the first 24 hours while in the intensive care unit.

Several mechanical compressive devices are available for use as DVT prophylaxis. Tight fitting knee-high or thigh-high antiembolic stockings reduce venous stasis in the leg, although some patients find them uncomfortable and difficult to tolerate. They should be used with caution in patients with significant peripheral arterial disease to avoid compromise of distal circulation. Alternatively, sequential pneumatic compression devices can be applied to the lower extremities of nonambulatory patients. The intermittent pumping action replicates normal muscular contractions used to move dependent venous blood against gravity. These cumbersome devices may increase the risk of falls when agitated or cognitively impaired patients attempt to get out of bed. They can also be time-consuming for staff to apply and monitor properly. A systematic review found insufficient randomized trial evidence to support the routine use of physical methods as the sole method for DVT prophylaxis in acute stroke (Mazzone et al, 2004). However, mechanical compression devices may be beneficial for patients with hemorrhagic infarcts or other conditions where the use of antithrombotics is contraindicated. Practically, many institutions use a combination

TABLE 4-2 Options for Deep Venous Thrombosis Prophylaxis

Method	Comment
Early mobilization	Close monitoring of blood pressure and neurologic status needed, especially during initial phases.
	May be difficult in patients with severe stroke.
Mechanical compressive devices • Antiembolic stockings • Sequential pneumatic compression devices	Useful for prophylaxis in those with contraindications to antithrombotic therapy and in the first 24 hours postthrombolysis. Caution in patients with severe peripheral arterial disease, peripheral neuropathy, or cognitive impairment.
Subcutaneous unfractionated heparin	Effective in reducing incidence of deep venous thrombosis/pulmonary embolism. Does not require monitoring. Hemorrhage risk may be concerning in patients with large strokes or history of systemic bleeding.
Low-molecular-weight heparins	Effective. Requires less frequent dosing. Risk/benefit ratio compared with unfractionated heparin unclear. Majority of benefit realized for asymptomatic venous thrombosis. Further studies needed.

KEY POINTS

- Measures to prevent deep venous thrombosis should be routine for all patients with ischemic stroke admitted to the hospital.
- The use of low-intensity anticoagulation for deep venous thrombosis prophylaxis is recommended for all immobilized patients with stroke.

of mechanical compression devices and pharmacologic regimens to reduce DVT risk.

The use of low-intensity anticoagulation for DVT prophylaxis is recommended for all immobilized patients with stroke (Adams et al, 2007). Clinical trials have evaluated various anticoagulation regimens for DVT/PE prophylaxis in acute ischemic stroke. Subcutaneously administered unfractionated heparin (UFH) and low-molecular-weight heparins have been demonstrated to reduce the risk of venous thromboembolic events after stroke. Concern for intracranial or systemic hemorrhage, particularly in patients with large ischemic strokes, has resulted in debate regarding the optimal timing and dosage of anticoagulation for venous thromboembolism prophylaxis. The results of pooled analyses suggest that low-molecular-weight heparins may offer a more favorable risk-benefit profile for reduction of DVT and PE compared with UFH after ischemic stroke; however, the conclusions are limited by study heterogeneity (Kamphuisen and Agnelli, 2007). Anticoagulants should not be used for 24 hours after administration of thrombolytic therapy. In patients with primary intracerebral hemorrhage, initiation of anticoagulation for DVT prophylaxis is often delayed for 3 to 4 days. However, definitive evidence to guide management after intracerebral hemorrhage is not available.

The Prevention of Venous Thromboembolism After Acute Ischaemic Stroke (PREVAIL) study attempted to clarify the optimal DVT prophylactic regimen after ischemic stroke. PREVAIL was a randomized, open-label comparison of daily subcutaneous enoxaparin 40 mg and twice-daily UFH 5000 international units for thromboprophylaxis in 1762 patients with ischemic stroke (Sherman et al, 2007). Eligible patients

KEY POINTS

- Given the limited benefit favoring enoxaparin for symptomatic thromboembolic events and the increased risk of symptomatic hemorrhage, definitive recommendations for routine practice cannot be made on the basis of the PREVAIL results.
- Fall prevention should be an important part of initial mobilization, and fall precautions should be used for appropriate patients with stroke.

had radiographically confirmed ischemic stroke and a measurable motor deficit in the leg that prevented independent ambulation (ie, high risk for DVT/PE). Treatment was initiated within 48 hours of symptom onset and continued for 10 days. The primary efficacy end point was a composite of symptomatic or asymptomatic DVT or symptomatic or fatal PE during the study treatment phase. The primary safety end points were symptomatic intracranial hemorrhage, major extracranial hemorrhage, and all-cause mortality up to 48 hours after treatment. A 43% relative risk reduction in the primary efficacy end point favored the group treated with enoxaparin. There was no statistically significant difference in the rates of intracranial hemorrhage between the two groups; however, the rate of major extracranial bleeding was higher with enoxaparin.

Although this study was well designed and attempted to answer a clinically important question, methodologic concerns have made interpretation of the results challenging. The diagnosis of DVT was made using the criterion standard method of bilateral contrast venography. Of the 189 venous thromboembolic events, 95% were clinically asymptomatic. The difference in the primary efficacy end point was largely due to the difference in rates of asymptomatic DVT identified on venography (10% for enoxaparin versus 17% for UFH) between the groups. The difference between treatment groups for symptomatic DVT (0.3% for enoxaparin versus 1% for UFH) or fatal PE was not significant. Major extracranial hemorrhage occurred in seven patients in the enoxaparin group and none in the UFH group ($P = .015$). Given the limited benefit favoring enoxaparin for symptomatic thromboembolic events and the increased risk of symptomatic hemorrhage, definitive recommendations for routine practice cannot be made on the basis of the PREVAIL results. Future trials of thromboembolic prophylaxis in acute ischemic stroke may yield more applicable results by focusing on symptomatic DVT as the primary efficacy outcome (O'Donnell and Kearon, 2007).

Falls

Fall prevention should be an important part of initial mobilization, and fall precautions should be used for appropriate patients with stroke. Patients with stroke are at relatively high risk for falls while hospitalized. A retrospective study including patients admitted to 23 hospitals found a fall incidence of 8.9 per 1000 patients per day (Tutuarima et al, 1997). The incidence of second falls was almost twice that of first falls. Heart disease, prestroke cognitive impairment, and urinary incontinence were identified as incremental risk factors for first falls. Most occurred during the day (45%), in the patient's room (51%), and during visits to the bathroom (20%). Slight to severe injuries were reported in approximately 25%, and hip fractures resulted in 2% of falls. Nurses can play an important role in minimizing falls by assessing fall risk at the time of admission, putting commonly needed items within hand's reach, keeping the bed in a low position, and encouraging the patient to ask for assistance. Additional measures to reduce fall risk are outlined in **Table 4-3**. Restraints and other physical devices should be avoided in agitated or cognitively impaired patients, as they do not effectively prevent falls and may worsen the severity of injury in those who fall (Shorr et al, 2002). Fall risk remains high during inpatient rehabilitation (Teasell et al, 2002), and preventive measures should continue after discharge to a rehabilitation facility.

Pressure Sores and Ulceration

Early mobilization of neurologically stable patients can help reduce the

TABLE 4-3 Measures to Prevent Falls in Hospitalized Patients With Stroke

- Use of adult assistive walking devices
- Motion detectors
- Bed alarms
- Use of convex mirrors to enable nursing staff to view hallways from nursing stations
- Nonslip footwear for patients
- Continuing staff education
- Minimal use of sedative medications

risk of pressure sores and ulceration. For patients who cannot be mobilized, routine assessment for skin breakdown, particularly in dependent areas, is recommended. Frequent turning can help minimize the risk of decubitus ulcers. Skin should be kept dry and free of moisture, particularly in patients with urinary incontinence. In some situations, oscillating mattress systems may be necessary to minimize prolonged pressure on susceptible areas (sacrum, greater trochanter). Antibiotics and debridement may be necessary in cases of severe skin breakdown.

Infections: Pneumonia and Urinary Tract Infections

Poststroke infection is common during the first 5 days after admission and is associated with worse short-term outcomes (Kwan and Hand, 2007). Fever is the heralding sign of infection in many patients and worsens prognosis after stroke (Azzimondi et al, 1995). Antipyretic agents should be administered to lower temperature in febrile patients with stroke while the source of the fever is ascertained (Adams et al, 2007). Patients with dysphagia are at high risk of aspiration pneumonia, but chest infection may develop in patients without frank aspiration events. A prospective study of hospitalized patients with stroke identified the following factors as independent predictors of pneumonia: age greater than 65 years, dysarthria or expressive aphasia (no speech), modified Rankin Scale score of 4 or greater, and failure of the bedside water swallow test (Sellars et al, 2007). Pneumonia negatively impacts functional outcomes and mortality after stroke (Aslanyan et al, 2004). Pneumonia occurred in 5.6% of patients after stroke in a recent study and was associated with a significantly increased cost of hospitalization and likelihood of extended care requirements upon discharge (Katzan et al, 2007). Appropriate evaluation of swallowing function and modification of oral intake may prevent many cases of pneumonia. General measures to prevent pneumonia include airway suction and aggressive pulmonary toilet in patients with reduced levels of consciousness. Incentive spirometry can facilitate air movement and prevent atelectasis at the lung bases. Mobilization and frequent changes in position may also help. A study of prophylactic antibiotics to prevent infection after stroke does not support their routine use (Chamorro et al, 2005). Prompt antibiotic therapy is warranted in patients with radiographically confirmed chest infection and in those where the clinical suspicion is high. Empiric coverage for both aerobic and anaerobic pathogens should be used to treat patients with presumed aspiration until results of cultures and sensitivities are available.

Urinary tract infection is another common infection in the hospitalized patient with stroke. The majority of urinary tract infections are associated with use of indwelling bladder catheters,

KEY POINT

- Urinary tract infection is a common infection in the hospitalized patient with stroke. The majority of urinary tract infections are associated with use of an indwelling bladder catheter.

KEY POINT

- Prior to allowing oral intake, a formal screen of swallowing function should be performed as part of the initial assessment of all patients with stroke.

which are often placed in immobilized patients for urinary retention or incontinence after stroke. Prolonged use of these catheters is discouraged because of their association with infection. Intermittent catheterization may be a reasonable alternative. Pharmacologic therapy with anticholinergic medications may help speed the return of bladder function; however, these agents should be used with caution given the potential for adverse cognitive effects. Routine urinalysis obtained as part of a fever evaluation will identify the majority of urinary tract infections. Prompt antibiotic treatment can help minimize the risk of bacteremia or sepsis.

Less common infections in the patient with stroke include cellulitis (in association with IV catheter placement or pressure ulcers) and cholecystitis. Endocarditis may be a causative factor in some ischemic stroke cases, particularly those involving IV drug use.

Dysphagia

Estimates of clinically apparent dysphagia after stroke range from 51% to 55% (Martino et al, 2005). Differences in reported estimates of poststroke swallowing dysfunction result from variable methods used for diagnosis (ie, clinical screening versus videofluoroscopy) and the timing of assessment in relation to stroke onset. A diverse array of stroke localizations may result in dysphagia. Hemispheric lesions may cause motor impairment of the face, lips, or tongue and/or attentional deficits that can compromise normal swallow function. Brainstem lesions can impair the normal coordination of pharyngeal swallow, laryngeal elevation, glottic closure, and cricopharyngeal relaxation. The consequences of dysphagia include aspiration and resultant chest infection (Martino et al, 2005), as well as dehydration, malnutrition, and difficulties with routine administration of medications.

Prior to allowing oral intake, a formal screen of swallowing function should be performed as part of the initial assessment of all patients with stroke. The presence or absence of the gag reflex does not reliably identify those at risk for aspiration. Several instruments and algorithms are available for bedside dysphagia screening, and the use of formal screening protocols can effectively prevent pneumonia (Hinchey et al, 2005). The presence of features listed in **Table 4-4** places patients at highest risk for dysphagia and aspiration. The 3-oz water swallow test is an appropriate screening tool (DePippo et al, 1992) for those without high-risk features. The patient is given 90 mL of water in a cup and asked to drink without interruption. If the patient is able to complete this task without a cough or change in voice quality, the patient can be cleared for oral intake. High-risk patients and those who fail the 3-oz water swallow test should be

TABLE 4-4 High-Risk Presentations for Dysphagia

- Brainstem stroke
- Impaired consciousness
- Difficulty or inability to sit upright
- Shortness of breath
- Slurred speech
- Facial weakness or droop
- Expressive aphasia
- Pneumonia
- Weak cough
- Hoarse voice
- Wet- or gurgly sounding voice
- Wet cough

maintained on a ''nothing by mouth'' status until formally evaluated by a speech pathologist. Improved outcomes have been demonstrated with early involvement of speech-language pathologists and management of patients with dysphagia by organized multidisciplinary teams (Smith Hammond et al, 2006). For patients requiring formal swallowing evaluation, antiplatelet therapy should not be delayed as per rectum (PR) preparations of aspirin are available. Emphasizing the importance of appropriate dysphagia screening to emergency department staff may reduce the likelihood of a patient inadvertently receiving food or drink prior to the swallow evaluation.

Patients who cannot safely take food or liquids orally may require a nasogastric or nasoduodenal tube to provide nutrition and medications. These measures, however, do not eliminate the risk of silent aspiration of oral secretions. Early institution of tube feedings has not proven beneficial in dysphagic patients (Dennis et al, 2005a). Many patients will demonstrate early improvement of their swallowing mechanism in the days following stroke. Therefore, repeated assessment to document changes in swallowing function will provide the opportunity to remove parenteral feeding tubes and advance of the diet as soon as possible. Patients whose need for tube feedings is anticipated to exceed 2 to 3 days may benefit from placement of a percutaneous endoscopic gastrostomy tube. These devices are usually more comfortable, require less care, and do not hinder rehabilitation efforts.

After appropriate dysphagia screening, measures should be taken to ensure adequate hydration and nutritional status. Malnutrition is associated with worse functional outcomes after stroke (Finestone et al, 1996). Daily calorie counts can help prevent malnutrition during an acute hospitalization. Randomized controlled trial data do not support the routine use of oral nutritional supplementation in patients who are able to swallow normally (Dennis et al, 2005b). Fluid balance should be monitored, and IV normal saline (0.9% NaCl [sodium chloride]) should be used to maintain adequate volume status in patients with restricted or limited oral fluid intake. Hypotonic saline should be avoided, as it may cause osmotic shifts of free water from the extracellular to the intracellular compartment and exacerbate peri-infarct edema.

KEY POINT

- High-risk patients and those who fail the 3-oz water swallow test should be maintained on a ''nothing by mouth'' status until formally evaluated by a speech pathologist.

Pain

Hemiplegic shoulder pain is a common complication in patients with significant proximal arm weakness. It has been associated with reduced functional recovery of the affected limb and increased rates of withdrawal from rehabilitation programs. Functional electrical stimulation, positioning programs, external shoulder support devices, and intraarticular steroid injections have been used with variable degrees of success in an attempt to reduce shoulder discomfort (Snels et al, 2002). The results of a randomized study suggested that therapeutic strapping of an ''at-risk'' hemiplegic shoulder limited development of shoulder pain during rehabilitation (Griffin and Bernhardt, 2006).

Headache has been associated with stroke in the acute/subacute phase in approximately 25% of patients (Jorgensen et al, 1994). Discomfort involving the cervical or lumbar spine, hip, knee, and/or ankle is common after stroke and during rehabilitation. Pain likely results from musculoligamentous injury with overuse, overstretching, or poor resting postures implicated as contributing factors. Anti-inflammatory medications and the use of orthotic devices when appropriate may minimize these complications.

Neuropsychiatric Disturbances

Depression has been reported to occur in up to 60% of patients within 3 months

KEY POINTS

- Depression has been reported to occur in up to 60% of patients within 3 months of stroke onset.
- A systematic review of nine prevention trials provided little support for the routine use of antidepressants to prevent depression after stroke.

of stroke onset. A series of patients assessed for the presence and severity of depressive symptoms within 3 weeks after first-ever symptomatic stroke found mild symptoms in 40% and moderate to severe depressive symptoms in 12% (Nys et al, 2005). This study found that the severity of depressive symptoms was related to lesion volume, functional impairment, and degree of overall cognitive impairment. A recent study attempted to identify the prevalence of poststroke mood disorders (anxiety/depression) within the first weeks after stroke and found 5% of hospitalized stroke survivors met criteria for a mood disorder within 2 to 5 days poststroke (Townend et al, 2007). The overall prevalence increased with subsequent evaluations up to 3 months and occurred despite improvements in disability.

Early initiation of antidepressants after stroke has been studied in an effort to minimize the development of mood disorders. A systematic review of nine prevention trials provided little support for the routine use of antidepressants to prevent depression after stroke (Hackett et al, 2005). Antidepressants with various mechanisms of action, including selective serotonin reuptake inhibitors, serotonin antagonist and reuptake inhibitors, and psychostimulants, were used in these trials. The duration of treatment varied from 2 weeks to 12 months. Pharmacotherapy did not have a definitive effect on mood scores, cognitive function, or disability. No significant differences in adverse event rates were seen in the treatment groups.

Acute confusional states (delirium), emotional lability, anxiety, and fatigue have been variably reported after stroke and may arise as a direct result of the ischemic injury or may be related to a general medical condition, such as an infection or electrolyte imbalance. The differential diagnosis of delirium is broad, and the causative factor(s) should be aggressively identified and addressed given the high morbidity and mortality associated with delirium. Predisposing factors include advanced age, preexisting cognitive impairment, and malnutrition. Withdrawal states should also be considered promptly as acute alcohol and benzodiazepine withdrawal can be life threatening. Benzodiazepines and antipsychotic medications can be used in cases of severe agitation or psychosis. Parenteral administration of thiamine may be beneficial in patients with poor nutritional status or a prior alcohol history. The clinical presentation of a typical patient with delirium is demonstrated in **Case 4-1**.

Miscellaneous Medical Complications

Many patients with stroke have comorbid cardiac disease and require surveillance for cardiac arrhythmias and myocardial ischemia. A standard 12-lead EKG is recommended as part of the initial stroke assessment, and continuous telemetry in the stroke unit can capture paroxysmal arrhythmias. Patients with cardiac symptoms or abnormal ST segments and/or T waves on EKG should have serial cardiac enzymes to exclude concurrent myocardial ischemia. Many patients with acute stroke will have echocardiography, which can assist in identifying structural heart disease.

Gastrointestinal (GI) bleeding was observed as a common complication in a large cohort of patients with acute ischemic stroke (Johnston et al, 1998). The risk of GI hemorrhage appears higher in older patients, those with greater stroke severity, and those with prestroke disability (Davenport et al, 1996). Currently, stroke guidelines do not recommend routine GI prophylaxis for all patients with stroke. Given the widespread availability of H2-antagonists

Case 4-1

A 78-year-old man was admitted to the hospital with an ischemic stroke involving the left internal capsule. Prior to hospitalization, he had been living in an assisted living facility because of mild dementia. Two days after admission he was noted to be agitated and ''confused'' on a routine nursing assessment. The examination was remarkable for an irritable, elderly man constantly attempting to get out of bed and trying to remove his IV access. Repeated attempts to calm and redirect him were unsuccessful. He was not oriented to the correct year, month, or date, and when asked why he was in the hospital he said, ''Because you buggers are holding me hostage here.'' He was febrile (38.5°C), tachycardic (heart rate 105), and had diffuse paratonia. The right hemiparesis noted on admission was unchanged. A noncontrast head CT demonstrated an area of hypodensity in the left posterior limb of the internal capsule and diffuse cerebral atrophy but no acute intracranial pathology. An EEG demonstrated diffuse slowing over all head regions without epileptiform activity. A urinalysis was remarkable for many white blood cells and bacteria.

Comment. Delirium is a common complication in hospitalized elderly patients, particularly those with preexisting cognitive impairment. It is often unrecognized, perhaps because it may develop rapidly and fluctuate between a hyperactive and hypoactive form. Common clinical features include inattention, disorganized thinking, alterations of consciousness, perceptual disturbances (eg, hallucinations, paranoia), and altered sleep-wake cycles. Diffuse paratonia and asterixis may accompany delirium of any cause. As noted previously, the etiology is often complex and multifactorial, involving precipitating factors superimposed on a vulnerable patient with predisposing conditions. In this case, the patient's age and preexisting cognitive impairment predisposed him to the development of an acute confusional state as a result of a urinary tract infection. Treatment of the urinary tract infection led to a return to the prior baseline over the course of 24 hours.

and proton-pump inhibitors, however, it is reasonable to use GI prophylaxis in stroke patients, particularly those who are unable to safely take food or liquids by mouth, as they appear at highest risk. Routine use of stool softeners can help prevent constipation.

PREVENTION AND TREATMENT OF ACUTE NEUROLOGIC COMPLICATIONS

Many patients hospitalized with acute stroke will experience a change in their neurologic status directly attributable to the stroke. The most frequent neurologic complications of stroke are listed in **Table 4-5**. A large series found that complications resulting in a measurable deterioration of neurologic function occurred in 13% of patients within 48 to 72 hours of hospitalization for acute ischemic

TABLE 4-5 Neurologic Complications in Hospitalized Patients With Stroke

- Cerebral edema
- Mass effect and herniation
- Hemorrhagic transformation
- Seizures
- Progressing ischemia
- Recurrent stroke

KEY POINTS

- Large infarctions involving the cerebral hemisphere or cerebellum may result in space-occupying mass effect due to cerebral edema.
- Clinically significant edema due to hemispheric infarction is relatively uncommon with an estimated frequency of up to 10% of ischemic strokes.

stroke (Weimar et al, 2005). Deterioration was attributed to progressive stroke (33%), increased intracranial pressure (27%), recurrent cerebral ischemia (11%), and secondary parenchymal hemorrhage (11%). Another series found that increased intracranial pressure (8%) and recurrent cerebral ischemia (5%) were the most common neurologic complications within the first week of hospital admission (Weimar et al, 2002).

Cerebral Edema and Mass Effect

Large infarctions involving the cerebral hemisphere or cerebellum may result in space-occupying mass effect due to cerebral edema. The neurologic deterioration observed in large hemispheric strokes results from transtentorial or uncal herniation. Extension of ischemia into adjacent vascular territories may occur as tissue shifts compress the anterior cerebral artery against the ipsilateral falx or the posterior cerebral artery against the incisura. Cerebellar infarction can result in brainstem compression and obstructive hydrocephalus when significant edema develops within the restricted confines of the posterior fossa. Progressive decline in the level of consciousness, worsening neurologic deficits, headache, and nausea or vomiting may herald the onset of clinically important edema (Ayata and Ropper, 2002). Drowsiness may be one of the earliest indicators. Life-threatening cerebral edema associated with massive middle cerebral artery (MCA) infarction typically becomes evident between 2 and 5 days after stroke onset (Hacke et al, 1996). However, significant edema can occur earlier. One case series found that neurologic deterioration within 24 hours occurred in 36% of patients with massive MCA infarction (Qureshi et al, 2003).

Clinically significant edema due to hemispheric infarction is relatively uncommon with an estimated frequency of up to 10% of ischemic strokes. The so-called malignant MCA syndrome is associated with mortality rates that approach 80% with conservative treatment (Hacke et al, 1996). Many of these strokes are caused by acute embolic occlusion of the distal internal carotid artery or proximal MCA. Considerable variability exists in the degree and timing of edema formation among patients. Reliable prediction of those at highest risk to develop life-threatening cerebral edema has proven difficult. Clinical variables associated with increased risk include a history of hypertension or heart failure and presence of leukocytosis (Kasner et al, 2001). A retrospective series that included autopsy data found younger age, female gender, absence of prior stroke history, higher heart weight, carotid artery occlusion, and an abnormal ipsilateral circle of Willis were more frequent in patients who developed brain swelling and herniation. Involvement of the superficial and deep MCA territory and infarction of the anterior cerebral/anterior choroidal territories occurred more frequently in those with deterioration (Jaramillo et al, 2006). The presence of hypodensity involving greater than 50% of the MCA territory and presence of the hyperdense MCA sign on noncontrast head CT sign have also been associated with neurologic deterioration (Manno et al, 2003). **Case 4-2** provides an example of the space-occupying mass effect after hemispheric cerebral infarction.

The optimal treatment of brain edema remains a controversial issue. Conventional medical approaches to the treatment of brain edema and elevated intracranial pressure are listed in **Table 4-6**. Randomized controlled trial data on the effectiveness

Case 4-2

A 48-year-old man was found by his wife to have left-sided weakness. He had fallen after attempting to get out of bed in the morning. Upon arrival to the emergency department, he was found to have a right head and gaze preference, left homonymous hemianopia, left hemiplegia, and left hemispatial neglect. The patient was last known to be neurologically normal the night before (greater than 8 hours previous) and was not eligible for acute stroke therapy. Over the ensuing 48 hours he became progressively more somnolent and was unarousable to noxious stimulus 72 hours after admission. The patient was intubated for airway protection, and an urgent noncontrast head CT was ordered (**Figure 4-1**).

Comment. The head CT clearly demonstrated an extensive area of infarction with associated mass effect in the right MCA territory. Young patients (aged less than 55 years) without significant cerebral atrophy are especially susceptible to the mass effect associated with large hemispheric infarction. Progressive transtentorial with brainstem compression often results unless medical or surgical means are instituted to control intracranial pressure.

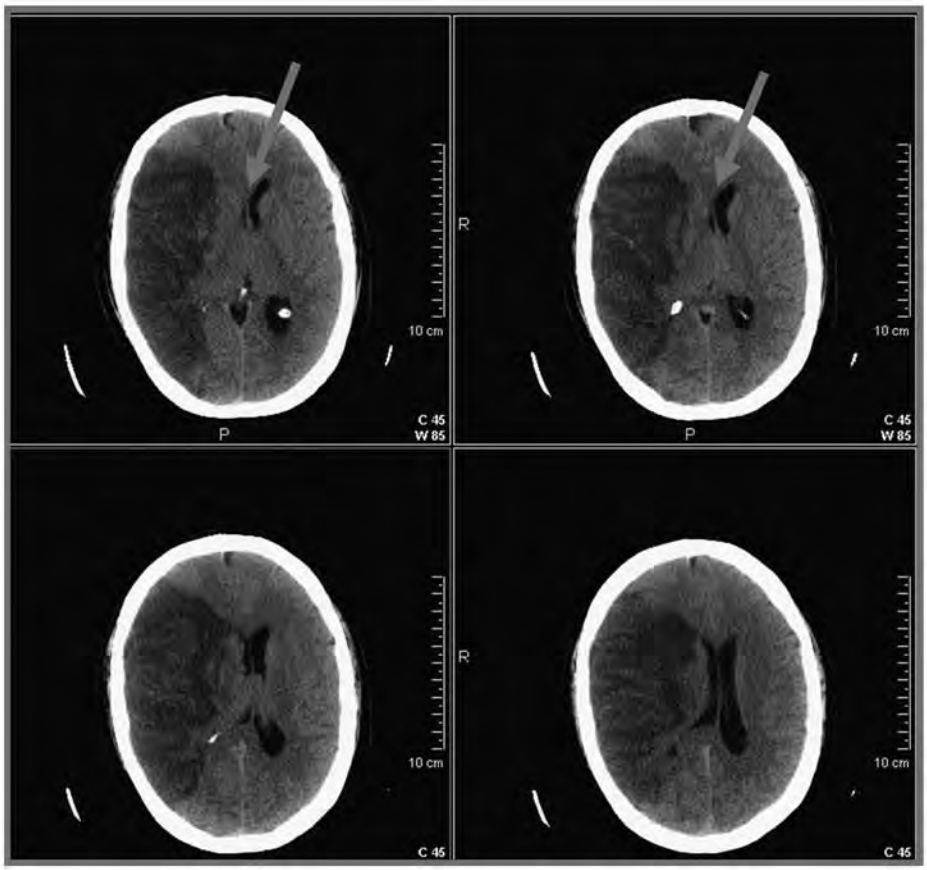

FIGURE 4-1 Sequential axial images from the noncontrast head CT demonstrate an extensive area of infarction with associated edema in the right MCA territory. The *arrows* indicate compression of the right frontal horn of the lateral ventricle and right-to-left shift of the septum pellucidum.

of these medical therapies to mitigate the effects of cerebral edema are not available (Bardutzky and Schwab, 2007). These strategies are often employed empirically or as a bridge to more definitive therapy in patients with neurologic deterioration. Consistent evidence supporting a beneficial effect on functional outcomes for these interventions is lacking.

Hemicraniectomy and duraplasty have been used as definitive therapy for life-threatening space-occupying edema. Decompressive surgery can

KEY POINT

- Hemicraniectomy and duraplasty have been used as definitive therapy for life-threatening space-occupying edema.

create space for the swollen brain to move out of the cranial cavity, rather than compressing critical brainstem structures (**Figure 4-2**). Because of the almost uniformly poor outcomes from the malignant MCA syndrome, decompressive surgery has been the subject of prospective evaluation. In order to provide the stroke community with safety and efficacy data in a

TABLE 4-6 Selected Medical Therapies for Cerebral Edema

Therapy	Comments
Mannitol	*Mechanism:* Osmotic agent—facilitates movement of fluid in the interstitial/intracellular compartment across the blood-brain barrier (ie, osmotic diuresis). May decrease blood viscosity. Preferential action at sites of intact blood-brain barrier raises theoretic concerns about shrinkage of normal tissue and exacerbation of tissue shifts. Serum osmolality usually targeted between 310 mosm/L and 320 mosm/L. 20% Mannitol: 1 g/kg initial bolus. Maintenance regimens use 0.5 g/kg or 0.25 g/kg every 4 to 6 hours.
Hypertonic saline	*Mechanism:* Osmotic agent—expands intravascular volume versus diuretic effect of mannitol. Similar concerns regarding exacerbation of tissue shifts due to necessity of intact blood-brain barrier for effect. Potential complications include hypernatremia, congestive heart failure, and pulmonary edema. Concentrations range from 3% to 23.4% saline with various bolus and continuous-dosing regimens.
Barbiturates	*Mechanism:* Decreases cerebral metabolism—subsequent reduction of cerebral blood volume and flow may reduce edema formation. Severe complications include hypotension (with impaired cerebral perfusion pressure), hepatic dysfunction, and increased infection risk. Limited and short-lasting benefit with potential for severe complications.
Hyperventilation	*Mechanism:* Induces cerebral vasoconstriction—subsequent reduction of cerebral blood flow and volume. Duration of benefit likely limited to a few hours. May reduce blood flow to near-ischemic levels. Potential for rebound vasodilatation and increasing edema and intracranial pressure. Partial pressure of carbon dioxide, arterial ($PaCO_2$) often targeted to $\sim$ 30 mm Hg.
Elevated head position	*Mechanism:* Increases venous outflow and reduces cranial venous hydrostatic pressure and volume. May cause decreased cerebral perfusion pressure due to decreased mean arterial pressure. Little evidence to support clinically meaningful benefit. Head of bed often kept at 30°.

Data from Bardutzky J, Schwab S. Antiedema therapy in ischemic stroke. Stroke 2007;38(11):3084–3094.

timely fashion, three European hemicraniectomy trials pooled their results and published the combined data prior to release of the individual trial results (Vahedi et al, 2007). All three trials restricted enrollment to patients aged 60 years or less with surgery performed within 48 hours of stroke onset. Ninety-three patients were randomized to surgical or medical therapy, and outcomes were assessed at 1 year with the modified Rankin Scale (mRS). The pooled analysis demonstrated the clear benefit of surgery on mortality with a 49% absolute risk reduction for fatal outcome favoring the surgical group (29% versus 78%). There was no difference between the groups in severely disabled survivors. The proportion of patients with minimal to moderate disability was significantly increased in the surgical group (43%) compared with the medical group (21%). No additional benefit was observed for patients undergoing surgery within 24 hours, and the benefits of surgery for prevention of death or moderate to severe disability was similar in patients with dominant and nondominant hemisphere infarctions. Prior to the publication of these results, many practices reserved hemicraniectomy for patients with clinical signs of herniation as a lifesaving ''salvage'' procedure. Traditionally, the procedure has not been offered to patients with dominant hemisphere infarction for fear of increasing the number of patients surviving in a severely disabled, aphasic condition. How these prospective data change current practice recommendations has yet to be established.

Following publication of the pooled analysis, the results of two of the individual hemicraniectomy trials have become available. DESTINY randomized 32 patients to either surgical or medical therapy and found a statistically significant reduction in mortality after 30 days favoring the surgical group (12% versus 53%) (Juttler et al, 2007). A nonsignificant benefit favoring surgery was seen for the primary end point of achieving an mRS of 0 to 3 (47% versus 27%). DECIMAL randomized 38 patients with malignant MCA infarction (aged less than 55 years) to hemicraniectomy or medical therapy (Vahedi et al, 2007). This trial required an additional radiographic criterion of a diffusion-weighted MRI lesion volume of greater than 145 cm^3 to establish eligibility. A statistically significant 52.8% absolute reduction in mortality favoring the surgical group was observed. A nonsignificant difference favoring surgery was found for the 6-month (25% versus 5.6%) and 12-month (50% versus

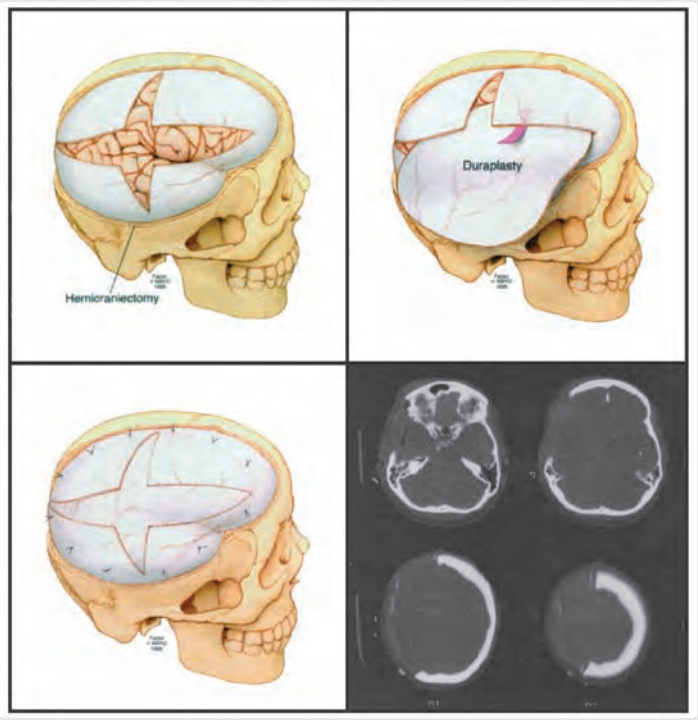

FIGURE 4-2 Schematic representation of decompressive hemicraniectomy. *Top left*, bone flap removed with cruciate dural incision. *Top right*, dural graft expands the intracranial compartment. *Bottom left*, the dura is fixed at the craniotomy margin, allowing the brain to herniate outwards with restoration of midline structures. *Bottom right*, CT bone window demonstrated the extent of skull removal.

Reprinted with permission from Wijdicks EF. Management of massive hemispheric cerebral infarct: is there a ray of hope? Mayo Clin Proc 2000;75(9):945–952.

KEY POINT

- Based on the results of a pooled analysis and the individual results from two trials, hemicraniectomy clearly improves survival after large middle cerebral artery territory infarction in selected patients and does not appear to increase the likelihood of severe disability in those who survive.

22%) functional outcomes of mRS of 3 or less. Based on the results of a pooled analysis and the individual results from two trials, hemicraniectomy clearly improves survival after large MCA territory infarction in selected patients and does not appear to increase the likelihood of severe disability in those who survive.

In addition to obstructive hydrocephalus caused by edema from cerebellar infarction, rapid deterioration may occur due to sudden apnea or cardiac arrhythmia associated with brainstem compression. The incidence of space-occupying edema with posterior circulation syndromes has not been well characterized. Results from case series demonstrate improved outcomes with the use of ventriculostomy and suboccipital craniectomy for patients with progressive clinical deterioration due to massive cerebellar infarction (Hornig et al, 1994). Although data are limited, current guidelines support the use of ventricular drains in patients with acute obstructive hydrocephalus and decompressive surgical evacuation for space-occupying cerebellar infarction (Adams et al, 2007).

Hemorrhagic Transformation

Another potential cause of neurologic deterioration after ischemic stroke is spontaneous hemorrhagic transformation of the cerebral infarction. Pathologic examination supports the notion that most cerebral infarctions have some degree of petechial hemorrhage on close inspection. However, this petechial blood is unlikely to be of any clinical significance. The exact frequency and risk factors that predispose to hemorrhagic transformation remain unclear. A systematic review of observational and clinical trial data with radiographic follow-up found an overall frequency of hemorrhagic transformation to be 8.5% in untreated patients. Hemorrhagic transformation accompanied by neurologic deterioration or frank hematoma formation occurred in 1.5%. The frequency was higher in patients treated with antithrombotic or thrombolytic drugs. Larger infarct size with mass effect and advanced age (greater than 70) were suggested as predisposing factors (Lindley et al, 2004).

Many patients with evidence of hemorrhagic transformation are managed conservatively with short-term discontinuation of antithrombotic agents and careful control of arterial blood pressure. Progressive neurologic deterioration due to hematoma-related mass effect may warrant emergent clot evacuation to prevent herniation.

Seizures

Estimates of seizure frequency after stroke based on retrospective analyses range from 2% to 23% (Adams et al, 2007). A prospective international study based on data from multiple centers reported seizures in 8.6% of patients after ischemic stroke (Bladin et al, 2000). In this cohort, a cortical location of infarction and stroke disability were independently associated with seizure occurrence. Cortical irritability caused by ischemic injury likely serves as the focus for partial seizures with or without secondary generalization. Patients with early-onset seizures (14 days or fewer poststroke) are at a lower risk of seizure recurrence than those with late-onset seizures (Berges et al, 2000). Status epilepticus may develop in a small proportion of patients with poststroke seizures and negatively impacts outcomes and mortality (Rumbach et al, 2000). Anticonvulsant therapy should be initiated in patients with witnessed or suspected seizures after stroke. The optimal duration of therapy has not been established. No studies have been designed to assess the efficacy of seizure prophylaxis after stroke. Prophylactic administration of anticonvulsants

to patients after stroke is not recommended (Adams et al, 2007).

STROKE UNITS

In contrast to many elements of post-stroke medical and neurologic care that are based on consensus guidelines, strong evidence supports the delivery of medical care after stroke within the structure of a specialized stroke unit. The concept of a stroke unit is based on the delivery of a disease-specific service in a geographically defined area of the hospital. These areas are staffed by multidisciplinary teams with specialized training in stroke and rehabilitation. Continuing educational programs for staff and involvement of caregivers in the education and rehabilitation process are also included in the model of a stroke unit. Monitoring capabilities allow close observation and recognition of changes in neurologic status or developing medical complications.

Stroke units are cost-effective, reduce mortality, and improve functional outcomes (Stroke Unit Trialists' Collaboration, 2002). The reduction in risk of death after stroke in patients who receive stroke unit care is likely achieved through the prevention and treatment of complications, particularly infections (Govan et al, 2007). The benefit of stroke unit care extends better outcomes across subgroups of all patients, regardless of age, sex, or severity of stroke. These advantages are also durable, with measurable beneficial effects extending to 10 years after stroke (Indredavik et al, 1999). In addition, the merits of stroke units can be replicated outside the confines of clinical trials (Seenan et al, 2007). Overall, the magnitude of benefit for stroke unit care may have greater population benefit than IV thrombolysis or other acute interventions (Gilligan et al, 2005).

CONCLUSION

Medical and neurologic complications after stroke are common, and preventive measures to reduce their frequency may have beneficial effects on stroke outcomes and neurologic recovery. Management of complications represents an important piece in the comprehensive care of the hospitalized patient with stroke. Close surveillance for signs or symptoms of complications related to immobility or infection is necessary. Neurologic deterioration should prompt assessment for cerebral edema, recurrent ischemia or hemorrhage, or seizure. Admission of stroke patients to specialized stroke units can help minimize the impact of medical complications. For those not eligible for acute stroke therapy, effective prevention and management of complications may provide the best opportunity to influence outcomes.

KEY POINTS

- Prophylactic administration of anticonvulsants to patients after stroke is not recommended.
- Stroke units are cost-effective, reduce mortality, and improve functional outcomes.

REFERENCES

Adams HP Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists [published errata appears in Stroke 2007;38(6):e38 and Stroke 2007;38(9):e96]. Stroke 2007;38(5):1655–1711.

Aslanyan S, Weir CJ, Diener HC, et al. Pneumonia and urinary tract infection after acute ischaemic stroke: a tertiary analysis of the GAIN International trial. Eur J Neurol 2004;11(1):49–53.

Ayata C, Ropper AH. Ischaemic brain oedema. J Clin Neurosci 2002;9(2):113–124.

Azzimondi G, Bassein L, Nonino F, et al. Fever in acute stroke worsens prognosis: a prospective study. Stroke 1995;26(11):2040–2043.

Bae HJ, Yoon DS, Lee J, et al. In-hospital medical complications and long-term mortality after ischemic stroke. Stroke 2005;36(11):2441–2445.

Bardutzky J, Schwab S. Antiedema therapy in ischemic stroke. Stroke 2007;38(11): 3084–3094.

Berges S, Moulin T, Berger E, et al. Seizures and epilepsy following strokes: recurrence factors. Eur Neurol 2000;43(1):3–8.

Bladin CF, Alexandrov AV, Bellavance A, et al. Seizures after stroke: a prospective multicenter study. Arch Neurol 2000;57(11):1617–1622.

Chamorro A, Horcajada JP, Obach V, et al. The Early Systemic Prophylaxis of Infection After Stroke study: a randomized clinical trial. Stroke 2005;36(7):1495–1500.

Davenport RJ, Dennis MS, Warlow CP. Gastrointestinal hemorrhage after acute stroke. Stroke 1996;27(3):421–424.

Dennis MS, Lewis SC, Warlow C; FOOD Trial Collaboration. Effect of timing and method of enteral tube feeding for dysphagic stroke patients (FOOD): a mulitcentre randomised controlled trial. Lancet 2005a;365(9461):764–772.

Dennis MS, Lewis SC, Warlow C; FOOD Trial Collaboration. Routine oral nutritional supplementation for stroke patients in hospital (FOOD): a multicentre randomised controlled trial. Lancet 2005b;365(9461):755–763.

DePippo KL, Holas MA, Reding MJ. Validation of the 3-oz water swallow test for aspiration following stroke. Arch Neurol 1992;49(12):1259–1261.

Finestone HM, Greene-Finestone LS, Wilson ES, et al. Prolonged length of stay and reduced functional improvement rate in malnourished stroke rehabilitation patients. Arch Phys Med Rehabil 1996;77(4):340–345.

Gilligan AK, Thrift AG, Sturm JW, et al. Stroke units, tissue plasminogen activator, aspirin and neuroprotection: which stroke intervention could provide the greatest community benefit? Cerebrovasc Dis 2005;20(4):239–244.

Govan L, Langhorne P, Weir CJ; Stroke Unit Trialists Collaboration. Does the prevention of complications explain the survival benefit of organized inpatient (stroke unit) care? further analysis of a systematic review. Stroke 2007;38(9):2536–2540.

Griffin A, Bernhardt J. Strapping the hemiplegic shoulder prevents development of pain during rehabilitation: a randomized controlled trial. Clin Rehabil 2006;20(4):287–295.

Hacke W, Schwab S, Horn M, et al. ''Malignant' middle cerebral artery infarction: clinical course and prognostic signs. Arch Neurol 1996;53(4):309–315.

Hackett ML, Anderson CS, House AO. Management of depression after stroke: a systematic review of pharmacological therapies. Stroke 2005;36(5):1098–1103.

Hinchey JA, Shephard T, Furie K, et al. Formal dysphagia screening protocols prevent pneumonia. Stroke 2005;36(9):1972–1976.

Hornig CR, Rust DS, Busse O, et al. Space-occupying cerebellar infarction: clinical course and prognosis. Stroke 1994;25(2):372–374.

Indredavik B, Bakke F, Slordahl SA, et al. Stroke unit treatment: 10-year follow-up. Stroke 1999;30(8):1524–1527.

Jaramillo A, Gongora-Rivera F, Labreuche J, et al. Predictors for malignant cerebral artery infarctions: a postmortem analysis. Neurology 2006;66(6):815–820.

Johnston KC, Li JY, Lyden PD, et al. Medical and neurological complications of ischemic stroke: experience from the RANTTAS trial. RANTTAS Investigators. Stroke 1998;29(2):447–453.

Jorgensen HS, Jespersen HF, Nakayama H, et al. Headache in stroke: the Copenhagen Stroke Study. Neurology 1994;44(10):1793–1797.

Juttler E, Schwab S, Schmiedek P, et al. Decompressive surgery for the treatment of malignant infarction of the middle cerebral artery (DESTINY): a randomized controlled trial. Stroke 2007;38(9):2518–2525.

Kahn SR. The post-thrombotic syndrome: progress and pitfalls. Br J Haematol 2006;134(4):357–365.

Kamphuisen PW, Agnelli G. What is the optimal pharmacological prophylaxis for the prevention of deep-vein thrombosis and pulmonary embolism in patients with acute ischemic stroke? Thromb Res 2007;119(3):265–274.

Kasner SE, Demchuk AM, Berrouschot J, et al. Predictors of fatal brain edema in massive hemispheric ischemic stroke. Stroke 2001;32(9):2117–2123.

Katzan IL, Dawson NV, Thomas CL, et al. The cost of pneumonia after acute stroke. Neurology 2007;68(22):1938–1943.

Kelly J, Hunt BJ, Lewis RR et al. Dehydration and venous thromboembolism after acute stroke. QJM 2004a;97(5):293–296.

Kelly J, Rudd A, Lewis R, Hunt BJ. Venous thromboembolism after acute stroke. Stroke 2001;32(1):262–267.

Kelly J, Rudd A, Lewis RR, et al. Venous thromboembolism after acute ischemic stroke: a prospective study using magnetic resonance direct thrombus imaging. Stroke 2004b;35(10):2320–2325.

Kwan J, Hand P. Infection after stroke is associated with poor short-term outcome. Acta Neurol Scand 2007;115(5):331–338.

Langhorne P, Stott DJ, Robertson L, et al. Medical complications after stroke: a multicenter study. Stroke 2000;31(6):1223–1229.

Lindley RI, Wardlaw JM, Sandercock PA, et al. Frequency and risk factors for spontaneous hemorrhagic transformation of cerebral infarction. J Stroke Cerebrovasc Dis 2004;13(6):235–246.

Manno EM, Nichols DA, Fulgham JR, et al. Computed tomographic determinants of neurologic deterioration in patients with large middle cerebral artery infarctions. Mayo Clin Proc 2003;78(2):156–160.

Martino R, Foley N, Bhogal S, et al. Dysphagia after stroke: incidence, diagnosis, and pulmonary complications. Stroke 2005;36(12):2756–2763.

Mazzone C, Chiodo GF, Sandercock P, et al. Physical methods for preventing deep vein thrombosis in stroke. Cochrane Database Syst Rev 2004;18(4):CD001922.

Nys GM, Van Zandvoort MJ, van der Worp HB, et al. Early depressive symptoms after stroke: neuropsychological correlates and lesion characteristics. J Neurol Sci 2005;228(1):27–33.

O'Donnell M, Kearon C. Thromboembolism prevention in ischaemic stroke. Lancet 2007;369(9571):1413–1415.

Qureshi AI, Suarez JI, Yahia AM, et al. Timing of neurologic deterioration in massive middle cerebral artery infarction: A multicenter review. Crit Care Med 2003;31(1): 272–277.

Rumbach L, Sablot D, Berger E, et al. Status epilepticus in stroke: report on a hospital-based stroke cohort. Neurology 2000;54(2):350–354.

Seenan P, Long M, Langhorne P. Stroke units in their natural habitats: systematic review of observational studies. Stroke 2007;38(6):1886–1892.

Sellars C, Bowie L, Bagg J, et al. Risk factors for chest infection in acute stroke: a prospective cohort study. Stroke 2007;38(8):2284–2291.

Sherman DG, Albers GW, Bladin C, et al. The efficacy and safety of enoxaparin versus unfractionated heparin for the prevention of venous thromboembolism after acute ischaemic stroke (PREVAIL Study): an open-label randomised comparison. Lancet 2007;369(9570):1347–1355.

Shorr RI, Guillen MK, Rosenblatt LC, et al. Restraint use, restraint orders, and the risk of falls in hospitalized patients. J Am Geriatr Soc 2002;50(3):526–529.

Smith Hammond CA, Goldstein LB. Cough and aspiration of food and liquids due to oral-pharyngeal dysphagia: ACCP evidence-based clinical practice guidelines. Chest 2006;129(1 suppl):154S–168S.

Snels IA, Dekker JH, van der Lee JH, et al. Treating patients with hemiplegic shoulder pain. Am J Phys Med Rehabil 2002;81(2):150–160.

Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. Cochrane Database Syst Rev 2002;(1):CD000197.

Teasell R, McRae M, Foley N, Bhardwaj A. The incidence and consequences of falls in stroke patients during inpatient rehabilitation: factors associated with high risk. Arch Phys Med Rehabil 2002;83(3):329–333.

Townend BS, Whyte S, Desborough T, et al. Longitudinal prevalence and determinants of early mood disorder post-stroke. J Clin Neurosci 2007;14(5):429–434.

Tutuarima JA, van der Meulen JH, de Haan RJ, et al. Risk factors for falls of hospitalized stroke patients. Stroke 1997;28(2):297–301.

Vahedi K, Hofmeijer J, Juettler E, et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. Lancet Neurol 2007;6(3):215–222.

Vahedi K, Vicaut E, Mateo J, et al. Sequential-design, multicenter, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL Trial). Stroke 2007;38(9):2506–2517.

Weimar C, Mieck T, Buchthal J, et al. Neurologic worsening during the acute phase of ischemic stroke. Arch Neurol 2005;62(3):393–397.

Weimar C, Roth MP, Zillessen G, et al. Complications following acute ischemic stroke. Eur Neurol 2002;48(3):133–140.

Wijdicks EF. Management of massive hemispheric cerebral infarct: is there a ray of hope? Mayo Clin Proc 2000;75(9):945–952.

EMERGING THERAPIES

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ABSTRACT

Acute stroke therapies are evolving gradually. The heterogeneity of stroke has made it difficult to achieve success in large randomized trials. There appears to be ''no shoe that fits all'' in stroke treatment other than early systemic thrombolysis using recombinant tissue-type plasminogen activator (rt-PA), which succeeds by achieving early recanalization, thereby limiting infarct extent. Many lessons have been learned that have refined our approach to developing new treatments. Emerging therapies for stroke can be classified into a few basic themes. In ischemic stroke, promising therapies are aimed at optimizing arterial recanalization through combined systemic drugs, ultrasound-enhanced treatment, or the use of interventional techniques, such as intraarterial tissue plasminogen activator, Merci® catheter, or a combined systemic/interventional approach. Neuroprotection treatment remains elusive, although strategies to initiate ultra-early (ambulance-based) neuroprotection appear justified. Collateral flow augmentation techniques appear promising in improvement of cerebral blood flow via this backdoor approach. The extension of treatment windows beyond the first 3 hours is reliant on neurovascular imaging techniques such as CT perfusion and multimodal MRI to detect significant penumbra.

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HYPERACUTE ISCHEMIC STROKE (LESS THAN 6 HOURS)

Early Recanalization Key to Good Outcome

The National Institute of Neurological Disorders and Stroke (NINDS) trials (Parts A and B) were the first and only major trials to demonstrate a clear benefit of IV recombinant tissue-type plasminogen activator (rt-PA) in acute ischemic stroke. Despite a 6.4% symptomatic intracranial hemorrhage rate, approximately 12% more patients recovered to independent outcome with treatment compared with placebo (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995). Most relevant to neurologists was the observed ''Lazarus effect'' (14-point improvement in stroke deficit score [NIH Stroke Scale]) in 20% of rt-PA-treated patients where dramatic neurologic improvement occurred within 24 hours compared with 3% of placebo-treated patients (Haley et al, 1997). The most important factor predicting benefit from rt-PA is early initiation of treatment, preferably within 90 minutes of onset (Marler et al, 2000). The benefit of thrombolysis clearly relates to recanalization of the occluded vessel (Rha and Saver, 2007). The magnitude of benefit from such

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Demchuk discusses the unlabeled use of emerging therapies with numerous references to potential therapies. Dr Gupta has nothing to disclose. Dr Khatri discusses the unlabeled use of the Merci Retriever® device and intraarterial rt-PA.

therapies is directly related to the speed that recanalization is achieved (Molina et al, 2004). Unfortunately, recanalization is not achieved early in a majority of patients treated with tissue plasminogen activator (t-PA). Proximal occlusions in arteries such as the distal internal carotid or proximal middle cerebral artery (MCA) infrequently recanalize with systemic t-PA in the first hours (del Zoppo et al, 1992; Saqqur et al, 2007).

Buying Time for Reperfusion—Ambulance-Based Neuroprotection

One approach to acute therapy is to develop treatments that ''buy time'' for the brain while waiting for recanalization to occur through the initiation of reperfusion strategies. Efforts to improve such neuronal survivability by neuroprotection treatment in acute stroke have failed for a variety of reasons, which include the complex multipathway nature of the ischemic cascade and late initiation of treatment. A single drug has limited ability to significantly halt the rapid and complex process of neuronal cell death when deprived of oxygen and glucose, particularly when given so late in the excitotoxicity process. Recent clinical trial benefit of early hypothermia-based neuroprotective therapy after cardiac arrest suggests continued hope for this field even in focal ischemia (Bernard et al, 2002; Hypothermia after Cardiac Arrest Study Group, 2002). The future for neuroprotection likely rests with ultra-early treatment initiated in the ambulance or when transport times are short in the first moments of emergency department arrival. The challenge of ambulance-based therapy is the heterogeneous population involved who are diagnosed as ''stroke.'' Many such patients spontaneously resolve en route (TIA) or may be misdiagnosed as stroke (seizure, hypoglycemia, etc). Very safe therapies with a wide therapeutic index are required for such an approach to limit toxicity risks if nonstroke patients are going to be inadvertently treated. Neuroprotection in the field offers the greatest likelihood to impact the penumbra at a time when such tissue is at its greatest extent. Such an approach should buy time by keeping neurons alive until careful attention to time of onset, medical history, and imaging criteria have determined suitability for initiating more definitive treatments aimed at restoring brain perfusion. The first clinical trial in this regard is the Field Administration of Stroke Therapy-Magnesium (FAST-MAG) trial based at Ronald Reagan UCLA Medical Center where IV magnesium sulfate is being tested (Saver et al, 2004). Similar approaches using high-flow oxygen therapy (hyperoxia) (Singhal, 2007) and hypothermia seem ideal for such an ambulance setting and could be combined in a cocktail approach with magnesium sulfate.

Improving Recanalization Through Systemic Drugs/Noninvasive Techniques

New systemic fibrinolytics. Novel agents that achieve higher recanalization rates and have greater safety with lower hemorrhage rates are the goal. Tenecteplase (TNK), a genetically modified form of t-PA, is one such agent with greater fibrin specificity, longer half-life, and greater resistance to inhibition by plasminogen activator inhibitor type 1 (Davydov and Cheng, 2001). The long half-life of TNK allows for single-bolus administration. A pilot dose-escalation safety study of TNK in patients with stroke demonstrated safety and tolerability of TNK at several doses with no symptomatic intracranial hemorrhages observed among any of the 75 patients treated at the lowest three dose levels (Haley

KEY POINTS

- Early recanalization is the key to achieving good outcome after ischemic stroke.
- Neuroprotective therapies will likely require ultra-early initiation that is ideal for the ambulance setting. Neuroprotection therapy's future lies with maintaining tissue salvageability during the additional time required for recanalization approaches.

et al, 2005). A large efficacy trial has now been initiated.

Desmoteplase is found in the saliva of the blood-feeding vampire bat *Desmodus rotundus*. Desmoteplase has 72% sequence homology with t-PA. In models of arterial thrombosis, desmoteplase induces faster and more sustained recanalization than t-PA and produces less antiplasmin consumption and fibrinogenolysis. Desmoteplase has shown mixed results in a series of phase 2 imaging-based trials in the 3 to 9 hours after-onset time window when a MRI diffusion-perfusion mismatch pattern is present (Hacke et al, 2005). Reteplase is a recombinant peptide with two similar domains to human t-PA but with a long half-life allowing for double-bolus injection. A small prospective study of intraarterial administration revealed high complete recanalization rates (Qureshi et al, 2001).

Combining fibrinolytics with antithrombotics. Embolic or thrombotic occlusions are resistant to systemic thrombolysis for many reasons, which include thrombus burden, high platelet content, resistance to rt-PA via plasminogen activator inhibitor, or nonthrombotic occlusion (dissection, calcium, etc) (**Table 5-1**). One strategy is to combine fibrinolytic agents such as rt-PA with other antithrombotic therapies such as heparin (Mikulik et al, 2006) or antiplatelet/glycoprotein (GP) IIb-IIIa antagonists (Pancioli and Brott, 2004, Seitz et al, 2004). This approach has a strong rationale, but published literature is limited. Prospective trials are currently underway, combining fibrinolytics with agents such as abciximab and eptifibatide, both highly selective GP IIb-IIIa antagonists that block platelet function.

Ultrasound enhancement of recanalization—combined IV treatments and ultrasound treatment. Experimental evidence suggests that ultrasound enhances thrombolysis and increases lytic effect of rt-PA, particularly if used in a low MHz or kHz frequency range. Ultrasound exposure causes various changes, such as reversible disaggregation of uncross-linked fibrin fibers (Braaten et al, 1997), microcavity formation in the shallow layer of thrombus, and increased enzymatic transport of rt-PA, improving its uptake and penetration of rt-PA into clots (Francis et al, 1995). Pilot work in acute stroke demonstrated an unusually high rate of ''on the table'' clinical responders coupled with early complete recanalization when continuous 2-MHz transcranial Doppler (TCD) was combined with IV rt-PA, raising the possibility that ultrasonic energy transmission by TCD was facilitating more rapid thrombolysis (Alexandrov et al, 2000). The phase 2 randomized controlled trial Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic t-PA (CLOTBUST) demonstrated an increase in complete recanalization or dramatic clinical recovery within 2 hours after rt-PA bolus in patients who were subjected to continuous ultrasound (Alexandrov et al, 2004). A new advance in this field is the development

TABLE 5-1 Factors Negatively Impacting Recanalization of Arterial Occlusion

- Large clot burden
- Blind alley or dead-end thrombus (no upstream or residual flow for systemic fibrinolytic)
- Nonthrombotic occlusion (calcium, dissection)
- Platelet-rich thrombus (less amenable to fibrinolysis)
- Very organized thrombus (fibrotic)

of nanobubbles. Nanobubbles were initially developed as contrast agents to enhance ultrasound signal detection. Nanobubbles, however, also adhere to the surface of clot and require ultrasound energy to cavitate and burst each nanobubble. As they fragment, jets of fluid and particles erode the adjacent clot. Recent data demonstrated improved recanalization rates with combined t-PA/ultrasound/nanobubbles compared with t-PA alone and t-PA/ultrasound (Molina et al, 2005). The first multicenter US Food and Drug Administration (USFDA)-registered safety study of therapeutic nanobubbles combined with IV t-PA and ultrasound is underway.

Neurointerventional Treatment to Enhance Recanalization

Intraarterial fibrinolytic therapy alone. Locally administered intraarterial fibrinolysis directly within thrombotic occlusions via direct microcatheter delivery offers several theoretical advantages over systemic fibrinolytic therapy. This includes attainment of higher concentrations of fibrinolytic agent at blood/thrombus interface, reduced systemic exposure to fibrinolytics, gentle mechanical manipulation or disruption of the clot by the microcatheter/guidewire, and precise imaging of vascular anatomy/collateral patterns. Disadvantages of intraarterial fibrinolysis include catheter manipulation within a vessel damaging or disrupting vessel wall integrity, heparin administration intraprocedurally to deter catheter-induced thrombosis, and delays in initiation of fibrinolysis caused by preparatory steps required for successful angiography and microcatheter positioning. The main drawbacks of intraarterial therapy are the labor and capital-intensive requirements only available at tertiary care centers.

The only large-scale, multicenter, randomized clinical trial of intraarterial fibrinolytic therapy alone demonstrated substantial clinical benefit of therapy initiated up to 6 hours after onset of an MCA stem (M1) or division (M2) occlusion. This Prolyse in Acute Cerebral Thromboembolism II (PROACT II) trial reflected pharmacologic lysis only because clot manipulation by microcatheter or guidewire was not permitted in the study (Furlan et al, 1999). Unfortunately the drug used in the study, prourokinase, is not available in regular practice because the results of the single PROACT II trial were insufficient to obtain USFDA approval. Despite a lack of randomized trials, rt-PA has been adopted as the fibrinolytic agent of choice for intraarterial application based on multiple large case-series cohorts suggesting reasonable safety profiles. The American Stroke Association guidelines recognize intraarterial fibrinolysis alone as a treatment option in select patients with large vessel occlusions.

Novel catheter-based devices to enhance recanalization. Novel catheter-based devices have also been evaluated to achieve recanalization either through improved clot dissolution or clot extraction. The devices are classified into three broad categories, which include endovascular thrombectomy (clot retrieval or suction aspiration), mechanical disruption (laser energy, angioplasty/stenting), and augmented fibrinolysis (catheter-tipped ultrasound). Unfortunately, use of most of the agents has been abandoned because of safety concerns or inflexibility limiting utility in the intracranial circulation. Repeated passage of a microguidewire through a thrombus is a simple form of mechanical disruption frequently undertaken during intraarterial fibrinolytic procedures and remains a mainstay approach. Primary intracranial angioplasty and carotid stenting are two promising endovascular reperfusion strategies in select clinical circumstances. Intracranial angioplasty appears particularly useful in patients

KEY POINTS

- Systemic treatments that could further enhance recanalization rates include new fibrinolytics, combination drug therapies, and ultrasound-enhanced thrombolysis.
- Interventional treatment can deliver fibrinolytics directly to the thrombus site with intraarterial thrombolytic delivery demonstrating efficacy in one major trial in the 0- to 6-hour time window.

KEY POINT

- Interventional treatment may also improve recanalization by specially designed catheters that aid clot dissolution or result in clot extraction via mechanical means.

with intracranial atherosclerotic lesions and supervening in situ thrombi (Ringer et al, 2001). Angioplasty achieves recanalization through controlled cracking and dissection of underlying atherosclerotic lesions. In a small case series, the more common spongy embolic material was also successfully ballooned open with soft silicone balloon angioplasty (Lum et al, 2006). Carotid stenting has been performed acutely in the setting of MCA stroke in the presence of cervical internal carotid artery occlusions with an 80% internal carotid artery recanalization rate (Nedeltchev et al, 2005).

The first USFDA-approved device for clot extraction in ischemic stroke is the Merci Retriever®, which is made of nitinol helix loops and retracted into a thrombus to ensnare the clot and then withdrawn within the device helix to allow aspiration of the clot. The Merci Retriever X5 and X6 devices were tested in the multicenter Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial in patients with internal carotid artery occlusion, M1 or M2 MCA occlusion, and vertebral and basilar artery occlusions within 8 hours of onset. Partial or complete revascularization was achieved by using the device alone in 54% with markedly improved clinical outcomes in those achieving recanalization. Symptomatic hemorrhage occurred in 5% of patients treated with the device; half were subarachnoid hemorrhage, likely due to vessel wall perforation by the catheter (Smith et al, 2005).

A second-generation Merci Retriever LX device was tested in humans in the multi-Merci clinical trial and achieved superior recanalization rates compared with the X5/X6 retriever. The Retriever LX has concentric helical loops with polymer filaments attached, increasing clot traction (Smith et al, 2006). **Figure 5-1** describes a case of Merci deployment with resultant recanalization of the MCA.

More recently, a Penumbra System™ has been developed, which removes the thrombus through two mechanisms: aspiration and extraction. A three-part system consisting of a reperfusion catheter, separator, and thrombus removal ring, the Penumbra System uses the principle of aspiration through a suction system. Thrombus material is aspirated from the occluded vessel into the catheter lumen and separated to maintain continuous suction. The thrombus removal ring is used to directly engage and remove the residual thrombus only if aspiration fails.

The Penumbra System has been tested in a prospective single-arm trial in patients presenting within 8 hours of symptom onset with an angiographically verified occlusion. Remarkably, all 21 of the treated vessels (100%) were successfully revascularized by the Penumbra System (Bose et al, 2008). **Figure 5-2** represents an example of the Penumbra System deployed in an MCA occlusion to achieve recanalization.

Combination IV and intraarterial thrombolytic therapy. Combining the advantages of systemic thrombolysis (speed of initiation and widespread availability) with intraarterial approaches (titrated dosage, mechanical manipulation of clot) appears very logical. Several pilot studies have been completed, assessing a combined approach of both IV and intraarterial t-PA treatment (Ernst et al, 2000; Lewandowski et al, 1999). The Interventional Management of Stroke (IMS) I trial evaluated the combined use of reduced-dose IV rt-PA, followed by microcatheter-delivered intraarterial rt-PA. This multicenter study demonstrated safety and acceptable rates of good outcome in selected patients with acute ischemic stroke, as compared with comparable subjects treated with full dose of IV rt-PA in the NINDS rt-PA Trial (The IMS Study Investigators, 2004).

The subsequent IMS II trial evaluated the EKOS MicroLysus® Ultrasound

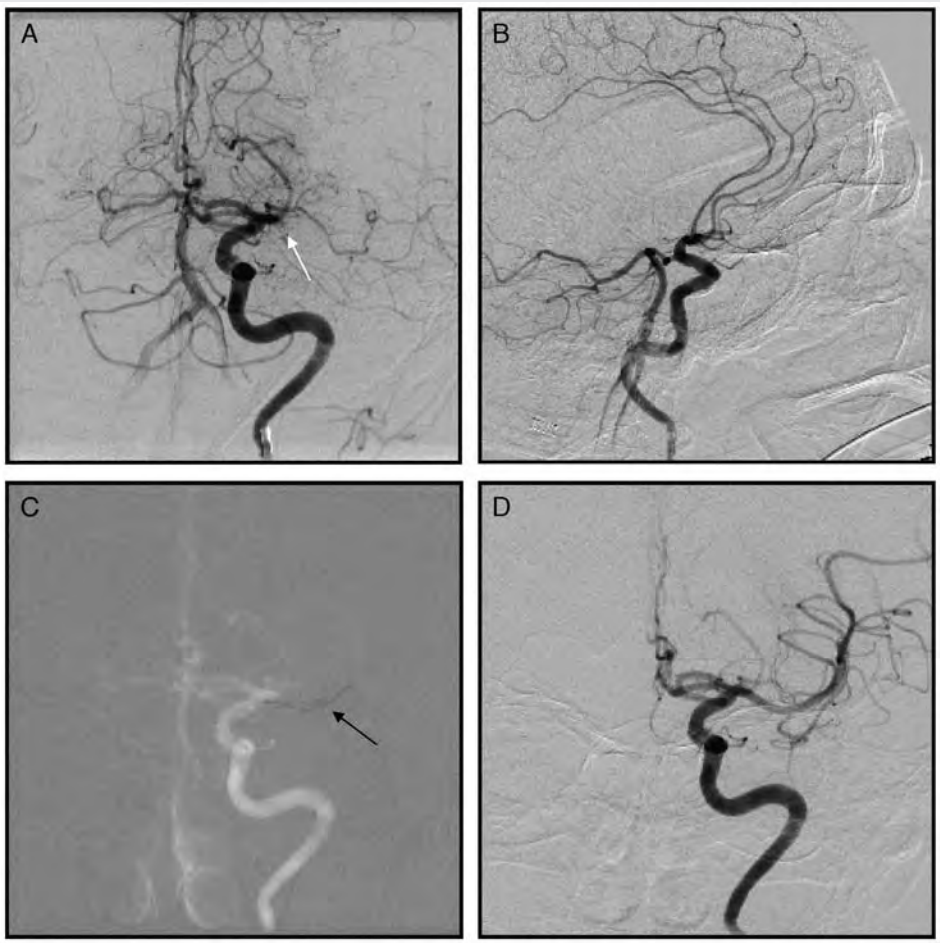

FIGURE 5-1 This is a 66-year-old woman who presented with an acute onset of global aphasia, right-sided hemiplegia, and left gaze preference 4 hours from symptom onset. She was taken emergently for angiography after an initial head CT without contrast showed no hemorrhage and no early ischemic changes. *A*, A left internal carotid artery injection shows an abrupt cutoff of the proximal left M1 portion of the middle cerebral artery (*white arrow*). *B*, A lateral projection shows absence of filling of the entire left middle cerebral artery territory. *C*, A roadmap image shows deployment of the Merci Retrieval® device (L5) (*black arrow*) in the left M1 segment of the middle cerebral artery. *D*, After one pass with the device, there is complete recanalization of the middle cerebral artery. The patient was found to have improvement in her neurologic examination 24 hours postprocedure. She was found to have a minimal aphasia with a mild dysnomia and moderate weakness of the right arm and leg. She was discharged to acute rehabilitation.

KEY POINT

- Combination IV thrombolysis and interventional treatment may offer the best of both worlds, with early initiation of treatment and optimized recanalization rates.

Catheter system, which is a small microcatheter with an ultrasound transducer tip that delivers ultrasound directly to the thrombus. When used in the study, the EKOS Primo sonography microcatheter achieved faster and more complete recanalization and reperfusion than standard microcatheter use in either IMS study (The IMS II Trial Investigators, 2007). The lesson from these two IMS pilot studies was that up to 18% of subjects may recanalize and reperfuse with reduced-dose IV alteplase alone, but that an additional 60% achieve distal perfusion when the EKOS-Ultrasound-assisted or standard microcatheter intraarterial rt-PA thrombolysis is also applied. IV rt-PA appears to "pick low-hanging fruit," leaving occlusions more amenable to interventional recanalization methods, such as intraclot thrombolysis, resulting in an overall reperfusion

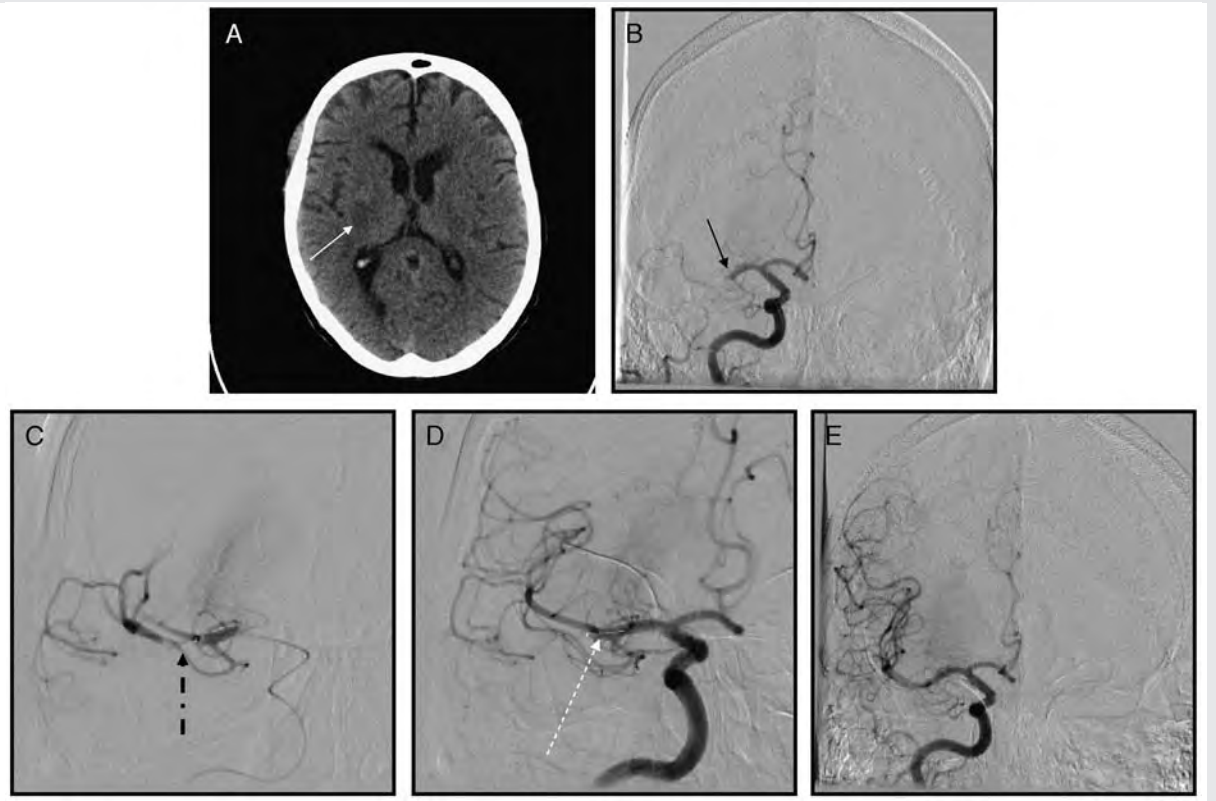

FIGURE 5-2 A 58-year-old man with a history of atrial fibrillation who discontinued his warfarin 2 weeks earlier for an elective colonoscopy presented with an acute onset of left-sided hemiplegia, right gaze preference, and a left-sided visual neglect. His symptom onset was 5 hours and 45 minutes earlier. *A*, An initial head CT showed a hypodensity (*white arrow*) in the right lentiform nucleus, and his Alberta Stroke Programme Early CT Score (ASPECTS) was tabulated at 8. *B*, Emergent angiography showed an occlusion of the right distal M1 segment of the middle cerebral artery (*black arrow*). *C*, A microcatheter was positioned in the thrombus, and selective angiography confirmed thrombus in the M1/M2 junction (*dotted black arrow*). *D*, A Penumbra™ aspiration catheter (*dotted white arrow*) was traversed into the thrombus to allow for aspiration thrombectomy of the clot. *E*, Complete recanalization of the middle cerebral artery postthrombectomy occurred. The patient had a marked improvement in his neurologic examination immediately postprocedure (''Lazarus effect'') with his only deficit being a mild left arm and left leg pronator drift.

rate approaching 80% (**Case 5-1**). The IMS-III is the first randomized trial comparing standard IV treatment with a combined IV t-PA and interventional treatment approach, which will include Merci catheter application at the discretion of the neurointerventionalist.

Collateral Flow Augmentation—Boosting Blood Flow Indirectly

One area that rarely attracts attention in stroke treatment is the collateral blood supply. This supply is the reason patients have salvageable ischemic brain in the penumbral zones of flow. Collateral flow is critical to successful recanalization, particularly in later time windows. Induced hypertension is one method to enhance collateral flow (**Case 5-2**). Changes in mean arterial blood pressure (MAP) within a range of about 50 mm Hg to 150 mm Hg did not affect cerebral blood flow (CBF) in normal individuals because of cerebral autoregulation (Waltz, 1968). Cerebral autoregulation, however, is impaired in ischemic brain, resulting in a linear increase in CBF with increases in MAP

Case 5-1

A 53-year-old man presented with sudden onset of left-sided paralysis and numbness with slurred speech. He arrived at the emergency department within 2 hours of last having been seen normal. His past medical history was limited to hypertension and elevated cholesterol. He had been taking two antihypertensive medications and a cholesterol-lowering agent. His neurologic examination revealed severe deficits consisting of right gaze paresis, left hemiplegia, left hemisensory loss, left hemineglect, and anosognosia. Laboratory tests were drawn and a CT scan performed that revealed only modest early ischemic changes in the right MCA territory and no evidence of hemorrhage. A CT angiogram revealed a right MCA occlusion in the M1 stem proximal portion of the vessel obstructing the lenticulostriate perforators. He had no contraindications to systemic thrombolysis. The risks and benefits of treatment were discussed with family, and a decision was made to proceed with treatment. IV rt-PA was injected based on estimated weight (0.9 mg/kg, with 10% as bolus, and the remaining over 1-hour infusion) at 2 hours and 40 minutes from symptom onset. Systolic blood pressure was kept below 185 mm Hg using antihypertensive therapy. No clinical improvement was seen over the first 20 minutes of rt-PA infusion.

Comment. This patient has received standard acute stroke treatment appropriately. Recanalization will result in the greatest benefit if it is achieved sooner. Major clinical improvement from early recanalization is expected in no more than about 25% of such patients with systemic treatment alone because of the large clot burden of an M1 MCA occlusion. Options include monitoring of this occlusion using TCD techniques to observe for recanalization. Additional therapeutic effect may also occur through ultrasound-enhanced thrombolysis. Other options include contacting the neurointerventional team and arranging for urgent angiography and consideration of interventional treatment. The exact timing of this decision is difficult. Systemic thrombolysis achieves early recanalization usually during the 1-hour rt-PA infusion; however, later recanalization has been reported with improved outcomes. Most interventional centers would agree to initiate interventional treatment if no major clinical improvement has been seen within the first 15 minutes of IV t-PA administration to limit time delays. Interventional treatment possibilities include using the Merci catheter (USFDA approved), administering additional rt-PA at the site of occlusion using microcatheter (not approved), wire manipulation of thrombus, or even angioplasty (not approved). Recanalization rates with combined IV and interventional treatment can approach 50% to 80%.

(Agnoli et al, 1968; Olsen et al, 1983). These studies led to the concept of using blood pressure elevation (induced hypertension) as a means of cerebral reperfusion.

Phenylephrine is the most commonly used agent for induced hypertension. It is a selective α_1-adrenergic receptor agonist that increases blood pressure by peripheral vasoconstriction, without increasing cardiac output or heart rate. It is administered intravenously and has a rapid onset and easy titration. In hypovolemic patients, major adverse effects include ischemic bowel and digital necrosis.

Case 5-2

A 75-year-old man presented with sudden onset of fluctuating symptoms of right-sided weakness and expressive speech difficulties. His symptoms were ongoing over the past 12 hours with several episodes of significant neurologic deficit separated by periods of mild neurologic symptoms. His past medical history was limited to hypertension and smoking. He had been taking three antihypertensive medications. In the emergency department he was witnessed to deteriorate substantially with significant neurologic deficits that included a severe nonfluent aphasia and loss of antigravity strength in his right arm. He was unable to extend his right wrist or fingers. A CT scan revealed no evidence of an acute infarct with only subtle early ischemic changes in the insula of the left MCA territory and no evidence of hemorrhage. A CT angiogram revealed a complete occlusion of the left cervical internal carotid artery. The left MCA was patent but appeared smaller in caliber compared to the right MCA. The internal carotid artery reconstituted from the left ophthalmic artery, and no posterior communicating artery was visualized. An anterior communicating artery was present, but the left A1 segment of the anterior cerebral artery appeared atretic. His blood pressure was 150 mm Hg systolic.

Comment. This patient has evidence of a large artery obstruction resulting in hemodynamic impairment of the left MCA territory, which causes fluctuating neurologic deficits. The absence of an infarct on CT despite 12 hours of symptoms suggested no or minimal ischemic core and a large region of brain at risk. Fibrinolytic therapy is not an option at this moment since the neurologic deficits have fluctuated for 12 hours without witnessed complete resolution. Acute carotid angioplasty and stenting of the carotid occlusion could be considered; however, this risks dislodging thrombotic material at the site of the cervical internal carotid artery occlusion into the distal internal carotid artery or MCA, resulting in further ischemic compromise. The most prudent option would be collateral blood flow augmentation with induced hypertension treatment. His blood pressure is not excessively high for this. A 10% to 20% increase in blood pressure should increase CBF in the ischemic left hemisphere. Significant neurologic improvement should be seen within 30 minutes of instituting phenylephrine infusion and would confirm a therapeutic response. A 1-day to 5-day stay in the neurointensive care unit could facilitate this treatment and allow for monitoring of complications. In time, collateral blood flow formation should develop or spontaneous recanalization of the cervical internal carotid artery occur, resulting in stabilization of symptoms.

Adequate hydration prior to initiation of IV phenylephrine and close clinical and telemetric monitoring are required to avoid complications such as congestive heart failure, renal failure, and digital ischemia. Phenylephrine has minimal effects on the cerebral vasculature (few α_1 receptors). Clinical experience with induced hypertension is limited to several-day therapy. Modest clinical improvement of neurologic deficits is frequently seen and occurs very quickly (2 to 30 minutes) after raising blood pressure. The frequency of clinical responses has been observed in over 50% of patients in these studies

(Hillis et al, 2003; Rordorf et al, 2001). Responses to induced hypertension were most often seen in the setting of previous TIA prior to stroke deficits, presence of large vessel occlusive disease, or fluctuating neurologic deficits (Rordorf et al, 1997). Further studies are needed to determine the optimal target blood pressure and the length of time that induced hypertension can be safely used, as well as to select the most appropriate patients.

Catheter-based collateral flow augmentation represents another emerging approach. An intraaortic balloon known as the NeuroFlo™ catheter device has been demonstrated to augment cerebral perfusion by redirecting flow to the cerebral circulation. The device produces a partial aortic obstruction with 70% balloon occlusion of the abdominal aorta proximal and distal to the renal arteries (Liebeskind, 2008). Phase 2 studies are now underway in a variety of clinical scenarios as either a stand-alone or adjuvant therapy.

Collateral flow augmentation with therapies such as induced hypertension or catheter-based flow diversion has potential to maintain cerebral perfusion by opening the collateral circulation as ''bridging therapy'' until recanalization of the occluded vessel occurs naturally or with therapeutic efforts. This bridge approach may be most useful in patients with instability of collateral circulation, manifesting as TIA, and fluctuating or progressive stroke (Caplan, 2002) (**Table 5-2**).

TABLE 5-2 Emerging Therapies in Ischemic Stroke Treatment

- **Enhance Early Recanalization**
  - Systemically
    - New fibrinolytics (tenecteplase, reteplase)
    - Combined t-PA + antithrombotics (glycoprotein 2bIIIa antagonists, heparin, etc)
    - Ultrasound enhanced (mHz +/- nanobubbles)
  - Interventionally
    - Intraarterial t-PA/clot manipulation
    - Clot dissolution devices (Penumbra™)
    - Clot extraction devices (Merci®)
- **Augment Collateral Flow**
  - Induced hypertension
  - Partial aortic obstruction
- **Ultra-early Neuroprotection**
  - Ambulance initiated: magnesium sulfate (Epsom salt), hypothermia, hyperoxia

t-PA = tissue plasminogen activator.

KEY POINT

- Collateral flow is critical to neuronal survival during ischemia. Augmentation of collateral flow via induced hypertension or downstream obstruction could allow more time for recanalization therapies to work.

ACUTE ISCHEMIC STROKE (GREATER THAN 6 HOURS)

Imaging-Based Selection for Recanalization Treatment Beyond Conventional Time Windows

The adage that ''time is brain'' reflects the extreme vulnerability of brain tissue to ischemia and the propensity for growing recruitment of the ischemic penumbra into the infarct core with prolonged vessel occlusion. However, the evolution of acute stroke is highly variable from patient to patient, and it is clear that a time-based thrombolysis strategy has limitations. Some patients who present within 3 hours of stroke onset will have well-developed infarction and little remaining ischemic penumbra, thus presenting a risk for hemorrhagic

KEY POINT

- Neurovascular imaging identifies penumbra beyond 3 to 6 hours from onset, which could aid selection of patients for recanalization therapies despite late time windows.

conversion following thrombolysis despite little expected tissue salvage. Alternatively, some patients who present many hours from symptom onset may have relatively small infarct cores with large areas of ischemic penumbra and may be ideal thrombolysis candidates, despite their exclusion from therapy based on the duration of their symptoms. This is evident in the pooled analysis of the four major thrombolysis trials demonstrating diminishing rates of return over time with treatment. Benefit is greatest within the first 3 hours but still seen up to 4.5 hours from onset with a 5% improvement in clinical outcome between 3 and 4.5 hours. No statistical benefit was seen 4.5 to 6 hours from onset (Hacke et al, 2004). Selection is critical to identify appropriate treatment candidates in later time windows. MRI and CT-based imaging methods provide this selection using a ''tissue-based'' treatment strategy. Both CT- and MRI-based studies can delineate the region of completed infarction (infarct core) as well as identify the ischemic brain tissue that can be salvaged with reperfusion (ischemic penumbra). It is important to emphasize that in any conceivable circumstance, it will always be crucial to institute therapy as soon as possible. Imaging to detect penumbra results in a tradeoff between obtaining more information and potentially adding to brain injury through delays in instituting therapy. The more sophisticated the imaging, the longer time required and the greater delay to instituting recanalization therapy. In the first few hours of stroke, most patients have significant penumbra, so complex imaging, such as multimodal MRI requiring 30 or more minutes for preparation and sequence acquisition, is difficult to justify and is unlikely to add significantly to treatment decision making. In late-presenting patients, however, a steadily decreasing proportion have substantial penumbra, and proper selection is critical, warranting sophisticated and highly accurate imaging of penumbra such as multimodal MRI.

Imaging-based penumbra detection for thrombolysis can be divided into three broad categories. It should be mentioned, however, that none of these penumbral imaging markers has been validated sufficiently or translated into definitive treatment approaches. One approach is the noncontrast CT/CT-angiogram paradigm, which we favor in Calgary because of its simplicity, practicality, and speed. This is based on evidence that infarct core can be visualized on noncontrast CT as early ischemic changes of hypoattenuation or loss of gray-white differentiation. Generally, when early ischemic changes are evident, the brain ischemia is irreversible and results in permanent infarct damage even with early recanalization. We apply the Alberta Stroke Programme Early CT Score (ASPECTS) scoring system to systematically evaluate the extent of early ischemic change within the MCA territory (Barber et al, 2000). Baseline ASPECTS scores have correlated closely to final infarct volumes (Demchuk et al, 2005). The penumbra is evaluated by detection of an intracranial occlusion using CT angiography, which can be performed immediately after noncontrast CT in a matter of minutes (less than 10 minutes from preparation to image reformats available for interpretation). When the extent of early ischemic change is modest (high ASPECTS score) and a proximal MCA occlusion is present, a state of significant ''penumbra'' is assumed. The main disadvantages to this approach are the difficulty visualizing early ischemic changes for the less experienced, limitations in CT angiography in detection of multiple distal

occlusions, and difficulties estimating penumbral size based on the site of occlusion, since this can be impacted significantly by collateral flow. This approach also fails to properly evaluate eloquent small volume lesions, such as lacunar stroke in locations such as the thalamus or internal capsule. Source images from CT angiography may provide an alternative to noncontrast CT early ischemic change detection as whole-brain cerebral blood volume (CBV)-weighted assessment reveals infarction with similar accuracy to diffusion-weighted imaging (DWI) and can be systematically evaluated using ASPECTS. Reevaluation of baseline CT scans in two thrombolysis clinical trials have confirmed the value of an ASPECTS-based noncontrast helical CT/CT angiography penumbral paradigm. Analysis of CT scans from the PROACT II study suggested that for patients with a proximal MCA occlusion and a baseline ASPECTS score greater than 7, there was a 3-times greater likelihood of a good outcome after treatment with intraarterial prourokinase compared to placebo, with a number needed to treat of 3 to 5 (Hill et al, 2003). Similarly, in an analysis of the IMS I pilot study of combined IV and intraarterial t-PA therapy for stroke, patients with an M1 MCA occlusion and an ASPECTS score greater than 7 were most likely to benefit from the combined approach (Hill et al, 2006). The intraarterial approach adds significant time to treatment, and a low ASPECTS score suggests the core is too extensive and penumbra too small to derive benefit from this combined approach in such patients. Validation of these findings will be evaluated in the IMS III trial.

A second and popular penumbral paradigm uses multimodal MRI in the form of DWI and perfusion-weighted imaging (PWI). Essentially, the DWI lesion is believed to highlight areas of cytotoxic edema in the infarct core, and PWI provides an assessment of cerebral perfusion deficits by assessing the dynamics of gadolinium contrast injection over a short period of time (approximately 60 seconds). Thus, in the DWI/PWI mismatch hypothesis, the differential volume between the DWI lesion and the PWI deficit represents ischemic penumbra that is potentially salvageable but will gradually be incorporated into the infarct core if reperfusion is not established. The diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study is the first trial to validate the value of DWI/PWI mismatch in thrombolysis therapy beyond 3 hours from onset. Good clinical outcomes were seen only in patients treated with thrombolysis who had DWI/PWI mismatch. Outcomes were not favorable in DWI/PWI-matched deficits or in patients with large DWI abnormalities (greater than 100 cc) (Albers et al, 2006). Most recently, the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) included multimodal MRI prior to randomization. This study of patients treated 3 to 6 hours after the onset of symptoms identified a trend toward clinical benefit of rt-PA over placebo in the DWI/PWI mismatch subgroup of patients (Davis et al, 2008). The challenges with multimodal MRI are time requirements and feasibility. A significant number of patients do not tolerate or cannot undergo multimodal MRI (Hand et al, 2005). A number of ongoing clinical trials are refining MR perfusion measures, exploring the validity of existing MR perfusion measures, and evaluating therapeutic impact of the DWI/PWI mismatch hypothesis with a variety of therapies, including desmoteplase, reteplase (Retevase)/abciximab, Merci catheter, rt-PA, and the Neuroflo aortic obstruction device.

KEY POINT

- A noncontrast helical CT/CT angiography-based ''good scan/occlusion'' approach to penumbra selection is practical and quick because of widespread CT angiography availability. Good scan is defined as minimal early ischemic changes or high ASPECTS score, and occlusion is defined as any symptom-relevant intracranial occlusion.

KEY POINTS

- Multimodal MRI perfusion-weighted/diffusion-weighted mismatch is the best studied imaging marker of penumbra in randomized clinical trials with promising results to date.
- CT perfusion cerebral blood volume/cerebral blood flow mismatch is another evolving penumbral imaging marker where cerebral blood volume abnormality equates with irreversible ischemic core, and the often larger cerebral blood flow abnormality surrounding the cerebral blood volume equates with the reversible ischemic penumbra.
- Basilar artery occlusion represents a special case where even late treatment thrombolysis or interventional treatment could be considered to achieve recanalization, given the uniformly poor prognosis otherwise.

The third penumbral paradigm uses CT perfusion (CTP) techniques that offer similar information without the logistical and availability issues that continue to plague MRI in acute stroke. CTP lesions with CBV values under 2.5 mL/100 g correlate well to DWI lesions, and, similarly, there is excellent correlation between CTP-defined ischemic penumbra (CBF reduction of 34% or more and CBV greater than 2.5 mL/100 g) and mean transit time lesions on PWI (Wintermark et al, 2002a). Vessel recanalization benefited patients clinically according to increasing proportion of CTP-defined ischemic penumbra (Wintermark et al, 2002b). Clinical trials validating this paradigm

Case 5-3

A 62-year-old woman presented with new onset of left-sided weakness and numbness and slurred speech. She arrived at the emergency department within 5 hours of last having been seen normal. She had been perfectly well when last seen by her husband. There was a delay to hospital presentation because she was alone at the time of the event and was subsequently found by her husband. She is not certain about the time her symptoms started. Her past medical history was limited to type 2 diabetes and a seizure disorder. She was only taking aspirin. Examination confirmed disabling deficits of left hemiplegia, left hemisensory loss, and dysarthria. Laboratory tests were drawn, and a CT scan performed, revealing no evidence of an acute or subacute infarct, no early ischemic changes in the right MCA territory, and no evidence of hemorrhage.

Comment. This patient represents a common quandary facing stroke physicians when patients present beyond the traditional systemic fibrinolysis time windows. The exact timing of ischemia in this case cannot be accurately estimated since no one witnessed when it occurred. It is possible the event had just occurred but this is supposition. This case illustrates the importance of imaging in determining whether reversible injury has occurred. The baseline noncontrast CT is helpful, as it suggests that the ischemic core is small or nonexistent. CT angiography would be the fastest approach to determining if penumbra exists, as any proximal intracranial occlusion would suggest a large zone of penumbra and the need for recanalization therapy, such as intraarterial thrombolysis or Merci catheter deployment. The absence of a large vessel occlusion would raise the possibility of a nonischemic cause, such as Todd paralysis, a lacunar event, or a distal embolic shower to the right hemisphere. Close evaluation of the posterior cerebral artery is required in such a patient, considering the deficits and the possibility of right thalamic involvement with a proximal posterior cerebral artery occlusion. Misinterpretation of the CT angiography can occur with the occasional M2 division occlusion of the MCA missed because of the presence of an MCA trifurcation or other anatomic variant/unusual anatomy. A normal CT angiogram might trigger additional imaging, although it is unlikely further therapeutic intervention would be considered. If performed, a normal multimodal MRI examination with no diffusion-weighted abnormality would certainly suggest a postictal Todd paralysis.

with reperfusion strategies are now underway.

Considering the importance of time, we favor a quick and simple approach in the first 6 hours from onset and prefer the noncontrast helical CT/CT angiography paradigm for difficult treatment decision making. At later time points or in situations where the lesion is suspected to be small volume (lacunar) or occlusions distal, we prefer the multimodal MRI paradigm (**Case 5-3**). In both cases additional clinical trial data are needed before widespread implementation of these penumbra imaging approaches can be recommended (**Table 5-3**).

TABLE 5-3 Penumbral Imaging Paradigms for Selection of Reperfusion Treatment (Beyond 3 Hours)

- **Rapid Noncontrast Helical CT/CT Angiography–Based "Good Scan/Occlusion" Paradigm**

  Good scan defined as noncontrast CT with minimal early ischemic changes (high Alberta Stroke Programme Early CT Score [ASPECTS]) + *occlusion*, defined as intracranial occlusion confirmed on CT angiography

- **Multimodal MRI Perfusion-Weighted Imaging/Diffusion-Weighted Imaging Mismatch Paradigm**

  Perfusion-weighted (Mean transit time, time to peak), volume abnormality at least 20% greater than diffusion-weighted abnormality

- **CT Perfusion Cerebral Blood Volume/Cerebral Blood Flow Mismatch Paradigm**

  Penumbra (CBF reduction of 34% or more and CBV greater than 2.5 mL/100 g) greater than core (CBV less than 2.5 mL/100 g)

CBF = cerebral blood flow; CBV = cerebral blood volume.

Basilar Artery Occlusion—the Special Case for Late Treatment

Patients with vertebrobasilar ischemia appear to represent a unique stroke population with potential for treatment beyond conventional time windows. Mortality in the setting of basilar artery occlusion is very high without intervention (Macleod et al, 2005). CT angiography provides rapid information on basilar artery occlusion status and is frequently used in the emergency assessment of patients with sudden coma or suspected vertebrobasilar ischemia (Brandt et al, 1999). Basilar artery recanalization is associated with good outcome (Arnold et al, 2004; Lindsberg and Mattle, 2006). Therapeutic approaches to basilar occlusion mirror those of MCA occlusion with recanalization the goal via whatever means necessary, including invasive interventional approaches.

CONCLUSION

In summary, neurologists are gradually gaining an arsenal of emerging treatments for acute ischemic stroke predominantly aimed at establishing early and complete recanalization. Ambulance-based neuroprotection and collateral flow augmentation offer potential adjuvant avenues of treatment. An assortment of imaging modalities are available to measure penumbra, which should aid selection of patients for recanalization strategies beyond the conventional 3-hour time window.

REFERENCES

Agnoli A, Fieschi C, Bozzao L, et al. Autoregulation of cerebral blood flow. Studies during drug-induced hypertension in normal subjects and in patients with cerebral vascular diseases. Circulation 1968;38(4):800–812.

Albers GW, Thijs VN, Wechsler L, et al. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. Ann Neurol 2006;60(5):508–517.

Alexandrov AV, Demchuk AM, Felberg RA, et al. High rate of complete recanalization and dramatic clinical recovery during t-PA infusion when continuously monitored with 2 MHz transcranial Doppler monitoring. Stroke 2000;31(3):610–614.

Alexandrov AV, Molina CA, Grotta JC, et al. Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke. N Engl J Med 2004;351(21):2170–2178.

Arnold M, Nedeltchev K, Schroth G, et al. Clinical and radiological predictors of recanalisation and outcome of 40 patients with acute basilar artery occlusion treated with intra-arterial thrombolysis. J Neurol Neurosurg Psychiatry 2004;75(6):857–862.

Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score [published errata appears in Lancet 2000;356(9235):2179]. Lancet 2000;355(9216):1670–1674.

Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346(8):557–563.

Bose A, Henkes H, Alfke K, et al. The Penumbra System: a mechanical device for the treatment of acute stroke due to thromboembolism. AJNR Am J Neuroradiol 2008;29(7):1409–1413.

Braaten JV, Goss RA, Francis CW. Ultrasound reversibly disaggregates fibrin fibers. Thromb Haemost 1997;78(3):1063–1068.

Brandt T, Knauth M, Wildermuth S, et al. CT angiography and Doppler sonography for emergency assessment in acute basilar artery ischemia. Stroke 1999;30(3):606–612.

Caplan LR. Worsening in ischemic stroke patients: is it time for a new strategy? Stroke 2002;33(6):1443–1445.

Davis SM, Donnan GA, Parsons MW, et al. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomized trial. Lancet Neurology 2008;7(4):299–309.

Davydov L, Cheng JW. Tenecteplase: a review. Clin Ther 2001;23(7):982–997.

del Zoppo GJ, Poeck K, Pessin MS, et al. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. Ann Neurol 1992;32(1):78–86.

Demchuk AM, Hill MD, Barber PA, et al. Importance of early ischemic change using ASPECTS in NINDS rt-PA Stroke Study. Stroke 2005;36(10):2110–2115.

Ernst R, Pancioli A, Tomsick T, et al. Combined intravenous and intra-arterial recombinant tissue plasminogen activator in acute ischemic stroke. Stroke 2000;31(11):2552–2557.

Francis CW, Blinc A, Lee S, Cox C. Ultrasound accelerates transport of recombinant tissue plasminogen activator into clots. Ultrasound Med Biol 1995;21(3):419–424.

Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. J Am Med Assoc 1999;282(21):2003–2011.

Hacke W, Albers G, Al-Rawi Y, et al. The Desmoteplase in Acute Ischemic Stroke Trial (DIAS): a phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. Stroke 2005;36(1):66–73.

Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS and NINDS rt-PA stroke trials. Lancet 2004;363(9411):768–774.

Haley EC Jr, Lewandowski C, Tilley BC. Myths regarding the NINDS rt-PA Stroke Trial: setting the record straight. Ann Emerg Med 1997;30(5):676–682.

Haley EC Jr, Lyden PD, Johnston KC, et al. A pilot dose-escalation study of tenecteplase in acute ischemic stroke. Stroke 2005;36(3):607–612.

Hand PJ, Wardlaw JM, Rowat AM, et al. Magnetic resonance brain imaging in patients with acute stroke: feasibility and patient related difficulties. J Neurol Neurosurg Psychiatry 2005;76(11):1525–1527.

Hill MD, Demchuk AM, Tomsick TA, et al. Using the baseline CT scan to select acute stroke patients for IV-IA therapy. AJNR Am J Neuroradiol 2006;27(8):1612–1616.

Hill MD, Rowley HA, Adler F, et al. Selection of acute ischemic stroke patients for intra-arterial thrombolysis with pro-urokinase by using ASPECTS. Stroke 2003;34(8):1925–1931.

Hillis AE, Ulatowski JA, Barker PB, et al. A pilot randomized trial of induced blood pressure elevation: effects on function and focal perfusion in acute and subacute stroke. Cerebrovasc Dis 2003;16(3):236–246.

Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346(8);549–556.

The IMS Study Investigators. Combined intravenous and intra-arterial recanalization for acute ischemic stroke: the Interventional Management of Stroke Study. Stroke 2004;35(4):904–911.

The IMS II Trial Investigators. The Interventional Management of Stroke (IMS) II Study. Stroke 2007;38(7):2127–2135. Epub 2007 May 24.

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(12):2598–2605.

Liebeskind DS. Aortic occlusion for cerebral ischemia: from theory to practice. Curr Cardio Rep 2008;10(1):31–36.

Lindsberg PJ, Mattle HP. Therapy of basilar artery occlusion: a systematic analysis comparing intra-arterial and intravenous thrombolysis. Stroke 2006;37(3):922–928.

Lum C, Stys PK, Hogan MJ, et al. Acute anterior circulation stroke: recanalization using clot angioplasty. Can J Neurol Sci 2006;33(2):217–222.

Macleod MR, Davis SM, Mitchell PJ, et al. Results of a multicentre, randomised controlled trial of intra-arterial urokinase in the treatment of acute posterior circulation ischaemic stroke. Cerebrovasc Dis 2005;20(1):12–17.

Marler JR, Tilley BC, Lu M, et al. Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. Neurology 2000;55(11):1649–1655.

Mikulik R, Dufek M, Goldemund D, Reif M. A pilot study on systemic thrombolysis followed by low molecular weight heparin in ischemic stroke. Eur J Neurol 2006;13(10):1106–1111.

Molina C, Ribo M, Arenillas JF, et al. Microbubbles administration accelerates clot lysis during continuous 2 MHz ultrasound monitoring in stroke patients treated with intravenous tPA. Stroke 2005;36:419.

Molina CA, Alexandrov AV, Demchuk AM, et al. Improving the predictive accuracy of recanalization on stroke outcome in patients treated with tissue plasminogen activator. Stroke 2004;35(1):151–156.

The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333(24):1581–1587.

Nedeltchev K, Brekenfeld C, Remonda L, et al. Internal carotid artery stent implantation in 25 patients with acute stroke: preliminary results. Radiology 2005;237(3):1029–1037.

Olsen TS, Larsen B, Herning M, et al. Blood flow and vascular reactivity in collaterally perfused brain tissue. Evidence of an ischemic penumbra in patients with acute stroke. Stroke 1983;14(3):332–341.

Pancioli AM, Brott TG. Therapeutic potential of platelet glycoprotein IIb/IIIa receptor antagonists in acute ischaemic stroke: scientific rationale and available evidence. CNS Drugs 2004;18(14);981–988.

Qureshi AI, Ali Z, Suri MF, et al. Intra-arterial third-generation recombinant tissue plasminogen activator (reteplase) for acute ischemic stroke. Neurosurgery 2001;49(1):41–48.

Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta analysis. Stroke 2007;38(3):967–973.

Ringer AJ, Qureshi AI, Fessler RD, et al. Angioplasty of intracranial occlusion resistant to thrombolysis in acute ischemic stroke. Neurosurgery 2001;48(6):1282–1288.

Rordorf G, Cramer SC, Efird JT, et al. Pharmacological elevation of blood pressure in acute stroke: clinical effects and safety. Stroke 1997;28(11):2133–2138.

Rordorf G, Koroshetz WJ, Ezzeddine MA, et al. A pilot study of drug-induced hypertension for treatment of acute stroke. Neurology 2001;56(9):1210–1213.

Saqqur M, Uchino K, Demchuk AM, et al. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. Stroke 2007;38(3):948–954.

Saver JL, Kidwell C, Eckstein M, et al. Prehospital neuroprotective therapy for acute stroke: results of the Field Administration of Stroke Therapy–Magnesium (FAST-MAG) pilot trial. Stroke 2004;35(5):e106–e108.

Seitz RJ, Meisel S, Moll M, et al. The effect of combined thrombolysis with rtPA and tirofiban on ischemic brain lesions. Neurology 2004;62(11):2110–2112.

Singhal AB. A review of oxygen therapy in ischemic stroke. Neurol Res 2007;29(2):173–183.

Smith WS. Safety of mechanical thrombectomy and intravenous tissue plasminogen activator in acute ischemic stroke: Results from the multi Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial, part 1. AJNR Am J Neuroradiol 2006;27(6):1177–1182.

Smith WS, Sung G, Starkman S, et al. The safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. Stroke 2005;36(7):1432–1438.

Waltz AG. Effect of blood pressure on blood flow in ischemic and nonischemic cerebral cortex: the phenomena of autoregulation and luxury perfusion. Neurology 1968;18(7):613–621.

Wintermark M, Reichhart M, Cuisenaire O, et al. Comparison of admission perfusion computed tomography and qualitative diffusion- and perfusion-weighted magnetic resonance imaging in acute stroke patients. Stroke 2002a;33(8):2025–2031.

Wintermark M, Reichhart M, Thiran JP, et al. Prognostic accuracy of cerebral blood flow measurement by perfusion computed tomography, at the time of emergency room admission, in acute stroke patients. Ann Neurol 2002b;51(4):417–432.

KEY POINTS

- Importantly, acute stroke care has undergone a transformation in the last decade.
- IV thrombolytic therapy is still very much underused, as only 2% to 8.5% of patients with stroke receive it.

PRIMARY STROKE CENTER CERTIFICATION

Steven R. Levine, David Adamowicz, Karen C. Johnston

ABSTRACT

Stroke is common, serious, and expensive. With the advent of a proven therapy for acute ischemic stroke as well as specific beneficial care processes and stroke prevention measures, there has been a groundswell of interest in developing stroke centers. The Joint Commission (formerly Joint Commission on Accreditation of Healthcare Organizations) has adopted stroke centers as a disease-specific initiative to oversee quality stroke care in America. Several states have initiated state-based designation procedures and policies. This chapter reviews the medical and financial issues related to the development of stroke centers, practical information for developing a stroke center at one's local hospital, and resources available to support this effort.

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INTRODUCTION

Presently in the United States, approximately 750,000 new or recurrent strokes occur every year, resulting in approximately 150,000 annual deaths. Stroke is the leading cause of long-term disability and the third leading cause of death in this country. Furthermore, its prevalence is increasing because the nation's population is aging. Importantly, acute stroke care has undergone a transformation in the last decade. The clear success of the 1995 National Institute of Neurological Disorders and Stroke (NINDS) recombinant tissue-type plasminogen activator (rt-PA) stroke trial led to the first, and to this day only, US Food and Drug Administration (USFDA)-approved drug for the treatment of acute ischemic stroke (National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995). rt-PA was shown to significantly improve patient outcome when delivered within 3 hours of symptom onset, with benefit lasting up to at least 1 year (Kwiatkowski et al, 1999).

IV thrombolytic therapy is still very much underused, as only 2% to 8.5% of patients with stroke receive it (Arora et al, 2005; Bambauer et al, 2006; Kleindorfer et al, 2003). Ideally, more than 40% of all stroke patients should receive rt-PA (Bambauer et al, 2006). Three major obstacles preventing additional rt-PA use have been proposed by Bambauer and colleagues (2006): (1) poor public awareness of stroke symptoms, (2) physician fear of legal liability, and (3) insufficient

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Levine discusses the unlabeled use of experimental therapies for stroke. Dr Adamowicz has nothing to disclose. Dr Johnston discusses the unlabeled use of investigational therapies.

funding for necessary facilities and personnel. Additional reasons include a lack of training for both neurologists and emergency medicine physicians in the use of the treatment, lack of adequate reimbursement for providing acute treatment (Kleindorfer et al, 2005), infringement of lifestyle for neurologists who are not well adapted to urgently arriving to an emergency department (ED) within a very brief period of time from notification, and the shortness of the allowable time window for administration of therapy (Kleindorfer et al, 2004) when there is not a cohesive and efficient emergency approach to acute stroke within a given hospital (Burgin et al, 2001).

THE STROKE CENTER CONCEPT

In 2000, the Brain Attack Coalition published recommendations for establishing primary stroke centers (PSCs) with the main goal of decreasing stroke-related mortality and morbidity (Alberts et al, 2000). The goal was to identify and certify hospitals that are equipped to treat patients with acute stroke with the intent of increasing the use of rt-PA and standardizing stroke care nationwide (Mohammad et al, 2006). A PSC is an establishment dedicated to providing organized and efficient care for patients with acute stroke.

Stroke centers are now officially recognized by The Joint Commission (formerly Joint Commission on Accreditation of Healthcare Organizations) and, therefore, have to abide by certain specific criteria. The specific certification process will be discussed later in this chapter. Further, several individual state departments of health have been designating PSCs in their state to improve prehospital triage and ambulance directives of acute stroke patients to hospitals properly committed to acute stroke care and rt-PA use. This chapter will review the procedure for earning PSC certification and the benefits that result from it. First, a discussion of the finances of stroke care placed within a historical context is provided as important background for the groundswell of interest in stroke care and treatment leading to the concept of the PSC and the need for public and professional education about stroke.

A HISTORY OF A SLOWLY IMPROVING FINANCIAL MISMATCH

For most of the period from June 1996, when the USFDA approved rt-PA for acute ischemic stroke, to today, hospitals and neurologists were not appropriately and adequately reimbursed for care and services provided for patients with acute stroke. ED physicians typically admitted acute stroke patients to primary care physicians, most often family practitioners and internists. Neurologist consultants saw the patient later that day or frequently the next day on rounds prior to going to the office to see outpatients and perform electrodiagnostic studies. This care model was generally acceptable to most clinicians because there was not proven, time-dependent treatment for acute ischemic stroke until the USFDA approval of rt-PA. This occurred despite physicians who care for acute stroke proclaiming ''time is brain'' (Gomez, 1993). More recent quantification of this concept suggests a loss of approximately 2 million neurons per minute during a typical large vessel occlusive stroke (Saver, 2006).

Slowly, a paradigm shift has evolved based on the significant financial benefit of rt-PA therapy to a health care system. More recently, hospitals benefited from a new, improved diagnosis-related group (DRG) reimbursement structure for patients with acute ischemic stroke treated with rt-PA (DRG

KEY POINTS

- Three major obstacles preventing additional recombinant tissue-type plasminogen activator (rt-PA) use have been proposed: (1) poor public awareness of stroke symptoms, (2) physician fear of legal liability, and (3) insufficient funding for necessary facilities and personnel.
- In 2000, the Brain Attack Coalition published recommendations for establishing primary stroke centers with the main goal of decreasing stroke-related mortality and morbidity.
- A primary stroke center is an establishment dedicated to providing organized and efficient care for patients with acute stroke.

KEY POINTS

- For most of the period from June of 1996, when the US Food and Drug Administration (USFDA)-approved rt-PA for acute ischemic stroke, to today, neurologists have not been appropriately and adequately reimbursed for care and services provided for patients with acute stroke.
- Slowly, a paradigm shift has evolved based on the significant financial benefit of rt-PA therapy to a health care system. Recently, hospitals have benefited from a new improved diagnosis related group reimbursement structure for acute ischemic stroke treated with rt-PA (DRG 559).

559) (**Figure 6-1**) (Demaerschalk and Durocher, 2007). With this financial paradigm shift, hospital administrators and health care business managers have begun to take acute stroke more seriously (as it positively impacted the bottom line). They have been more willing to partner with physician leaders to develop acute stroke care protocols that incorporate rt-PA within a hospital emergency setting. Administration has provided, at times, some of the resources needed to provide this heightened level and multidisciplinary complexity of care (Steven R. Levine personal experience with affiliated community hospitals and informal survey of stroke neurologists nationally).

IV rt-PA was first found to be cost-saving by Fagan and colleagues (1998): a cost savings of $4 million per 1000 patients treated. Demaerschalk and Yip (2005) performed a financial modeling analysis on the incremental impact of greater utilization of rt-PA. If the proportion of acute ischemic stroke patients receiving rt-PA were increased to 4%, 6%, 8%, 10%, 15%, or 20%, the realized cost savings would be approximately $15, $22, $30, $37, $55, and $74 million, respectively. This increase would result in an enormous realized savings for America's health care system.

PRACTICAL IMPACT ON PHYSICIAN BILLING

The American Academy of Neurology (AAN) recommends that physicians bill using *Current Procedural Terminology (CPT)* evaluation and management (E/M) codes (99221-99223 for initial hospital care, 99291-99292 for critical care, and 99356-99357 for prolonged inpatient service). The AAN's stroke coding guide encourages the

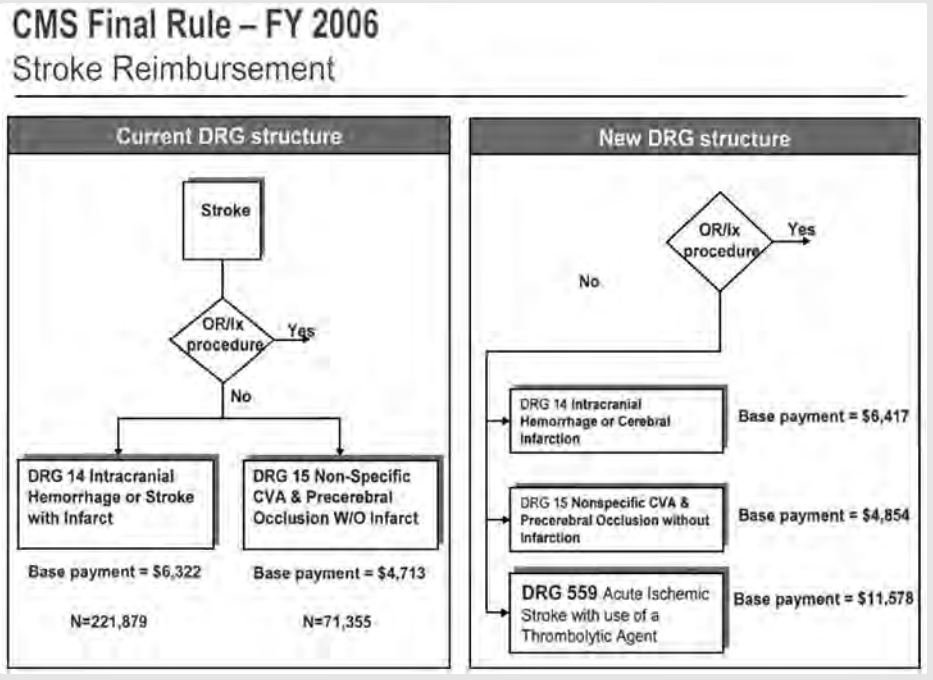

FIGURE 6-1 Revised US federal government diagnosis related group reimbursements for acute ischemic stroke.

DRG = diagnosis related group; OR/Ix = operating room/interventional; CVA = cerebrovascular accident.

Data from Centers for Medicare & Medicaid Services, Medicare Provider Analysis and Review (MEDPAR), 2003.

use of the critical care codes for stroke with appropriate documentation of time. Recommendations from others include use of E/M codes 99251 to 99255 for the initial inpatient consultation. Codes for rt-PA administration (37195), physician standby services (99360), and phone consultations (99371-99373) are not covered by Medicare and many private insurance companies. Code 37195 is not covered because it does not contain a physician work value because oftentimes rt-PA is administered by hospital staff. Two attempts to combine these *CPT* codes in 2002 to bill for rt-PA administration calculated reimbursement rates between $445 and $460 (Bambauer et al, 2006). These reimbursement rates are similar to reading four electroencephalograms, injecting botulinum toxin into either an arm or a leg, and spending 1 hour with a critically ill stroke patient. The clinician summary of the AAN coding guideline for stroke and critical care is available at *www.aan.com/globals/axon/assets/2858.pdf* and included as an **Appendix**.

Incentivizing Physicians to Perform Acute Stroke Care

There is clearly a problem trying to provide a financial incentive that outweighs the liability concern for a neurologist managing acute rt-PA treatment in an emergency setting. Either the ED or the neurologist, but not both, can bill for the rt-PA treatment procedure. The lack of reimbursement for some of the relevant E/M codes, combined with a major cloud of potential liability and lawsuits, creates little incentive for busy neurologists to interrupt other work or personal time to help EDs provide rt-PA.

Two years ago, the US Centers for Medicare & Medicaid Services created DRG code 559 to increase reimbursement for stroke patients treated with rt-PA—almost doubling the reimbursement rate for a similar stroke patient not given rt-PA. This was a critical step in facilitating hospital and neurologist involvement in providing this proven therapy. The current reimbursement policy, however, falls short for patients treated in a ''drip and ship'' fashion (ie, patient is given IV rt-PA bolus at one hospital and transferred during IV infusion to a second hospital). Only the facility that initiates treatment can bill and be reimbursed while the receiving hospital, despite taking on the brunt of the postthrombolysis care, cannot be reimbursed for the thrombolytic care through DRG 559. It is important to note, however, that effective October 1, 2008, a new *International Classification of Diseases, Ninth Revision (ICD-9)* v-code became available that should be used to track cases in which the patient receives rt-PA at one facility and is then transferred and admitted to another facility (V45.88 Status postadministration of t-PA [rt-PA] in a different facility within the last 24 hours prior to admission to current facility; code first condition requiring t-PA administration, such as: acute cerebral infarction [433.0-433.9 with fifth digit 1, 434.0-434.9 with fifth digit 1] acute myocardial infarction [410.00-410.92]). Hospital staff need to use this code so that these cases can be tracked and data gathered to assess the need for a new DRG to address the payment disparity.

While movement in the direction of a more systematic, coordinated, multidisciplinary approach to stroke has been taking place across the United States over the past decade, many community hospitals have still not been able to identify specialty physician leaders (preferably ED physicians or neurologists) who champion stroke care in their hospital and work hand in hand with a facilitative administrator

KEY POINTS

- There is clearly a problem trying to provide a financial incentive that outweighs the liability concern for a neurologist managing acute rt-PA treatment in an emergency setting.
- While movement in the direction of a more systematic, coordinated, multi-disciplinary approach to stroke has been taking place across the United States over the past decade, many community hospitals have still not been able to identify specialty physician leaders who champion stroke care and can work hand in hand with a facilitative administrator to optimize stroke care.

KEY POINT

- The establishment of primary stroke centers has the potential to improve the care of patients with stroke.

to optimize stroke care. This seems to be a particular problem in the more rural nonurban hospitals where a relative lack of protocol-driven, evidence-based stroke care has been highlighted (Burgin et al, 2001).

WHAT IS A PRIMARY STROKE CENTER?

The idea of a stroke center was based on scientific medical literature that demonstrated advantages of several treatments and approaches to acute stroke care. The evidence, derived from both randomized clinical trials and observational studies, suggests that several elements of a stroke center would improve patient care and outcomes (**Table 6-1**).

The stroke center designation first became available in November 2003, and currently more than 500 programs carry it (Joint Commission, 2008).

Key elements of PSCs include acute stroke teams, stroke units, written care protocols, and an integrated emergency response system. Important support services include availability and interpretation of CT scans 24 hours every day and rapid laboratory testing. Administrative support, strong leadership, and continuing education are also important elements for stroke centers. Adoption of these recommendations may increase the use of appropriate diagnostic and therapeutic modalities and reduce peri-stroke complications. The establishment of PSCs has the potential to improve the care of patients with stroke (Lattimore et al, 2003). One of the most important challenges is coordinating a multidisciplinary approach to acute stroke that involves hospital administration, emergency physicians and nurses, neurologists, dedicated stroke beds/unit with appropriate monitoring, radiology, laboratory, pharmacy, patient transport, and rehabilitation.

Necessary Components

Many hospitals do not have the necessary infrastructure and organization to treat patients with stroke rapidly and efficiently. With this fact in mind, the Brain Attack Coalition has identified 11 criteria that are necessary for establishing a PSC. These can be subdivided into two groups: patient care areas and support services.

The former group includes acute stroke teams, which would be composed of a variety of health care professionals who have experience with cerebrovascular disease. They can take alternating shifts, but there must be at least one physician, along with

TABLE 6-1 Major Elements of a Primary Stroke Center

▶ **Patient Care Areas**
Acute stroke teams
Written care protocols
Emergency medical services
Emergency department
Stroke unit[a]
Neurosurgical services
▶ **Support Services**
Commitment and support of medical organization; a stroke center director
Neuroimaging services
Laboratory services
Outcome and quality improvement activities
Continuing medical education

[a]A stroke unit is only required for those primary stroke centers that will provide ongoing in-hospital care for patients with stroke.

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another professional, available 24 hours a day, every day. The teams would have a system for rapid notification and activation of a stroke code so that they can be at the patient's bedside within 15 minutes of admission. The average annual cost for the stroke teams would range from $5000 to $10,000, depending on their size. There should be written documentation of the existence of the teams with a description of their role, and a log should be kept for quality improvement purposes. Financial incentives need to be considered (**Table 6-2**).

The next criterion is written care protocols, which are needed for the emergency care of patients with ischemia or hemorrhage. There must also be treatment-specific protocols, such as one for the use of rt-PA. The protocols should be available in the ED, and they should be updated once a year. Recording adherence to these protocols can help improve quality on a continuous basis. Examples include preprinted admission order sets with checkboxes that prompt the provider to address the necessary elements of stroke care, such as deep vein thrombosis prophylaxis, dysphagia screening, and physical and occupational therapy consultations. Additionally, tissue plasminogen activator (t-PA) order sets reduce t-PA-related complications by enforcing inclusion and exclusion criteria.

Emergency medical services (EMS) must be available to provide timely care to patients. Stroke has to be classified as a high priority in order to make rapid access possible, which has been shown to be beneficial for patient outcome. EMS must be integrated within the center itself and can cooperate in education initiatives that are launched by the center. Finally, EMS must have a written plan of action to which it should adhere as closely as possible.

Getting Started

What are the Joint Commission requirements? The Joint Commission has a disease-specific care certification

TABLE 6-2 Ways to Improve Financial Incentives for Using Recombinant Tissue-Type Plasminogen Activator to Treat Stroke Patients[a]

- Allowing simultaneous reimbursement for multiple providers from multiple specialties who contribute on the same day to a patient's stroke treatment
- Providing Medicare reimbursement for all relevant *CPT* codes
- Encouraging private insurance reimbursement of these *CPT* codes
- Creating new *CPT* codes for acute resuscitative and chronic stroke care
- Modifying DRG code 014 reimbursement rates to reflect costs of modern stroke treatment.

[a]Recommended by the 2002 National Institute of Neurological Disorders and Stroke report ''Incentives for Enhancing Stroke Care.''

CPT = *Current Procedural Terminology*; DRG = diagnosis related group.

Data from Schneider SM, Goldstein LB, Adams JG, et al. Improving the chain of recovery for acute stroke in your community: task force report. Incentives for enhancing stroke care. *www.ninds.nih.gov/news_and_events/proceedings/stroke_2002/acute_stroke_incentives.htm.* Updated July 15, 2008. Accessed August 1, 2008.

TABLE 6-3 Joint Commission Standardized Measure Set Framework

Domains	Key Measurement Areas
Urgent care assessment	• Stroke team • Written care protocols • Initial physical assessment and neurologic evaluation Ischemic versus hemorrhagic stroke Vital signs • Diagnostics Blood counts, coagulation, chemistry EKG Chest x-ray Vascular imaging Brain imaging
Acute care hospitalization/ treatment	• Airway/ventilatory support • Anticoagulation • Rehabilitation referral • Antiplatelet therapy • Antithrombotic therapy • Avoidance of nifedipine • Deep vein thrombosis prophylaxis
Risk factor modification	• Smoking • Obesity • Alcohol intake • Heart disease • Sedentary lifestyle/physical activity • Diet
Secondary prevention	• Hypertension • Medications • Carotid artery disease • Smoking cessation • Diabetes • High cholesterol • History of TIA
Education	• Cause of stroke • Adherence to medication use • Resources for social support or services • Risk factor modification/healthy lifestyle • Treatment of stroke • Discharge preparation
Rehabilitation	• Instrumental activities of daily living • Multidisciplinary evaluations • Speech therapy Dysphagia Speech and oral expression Aphasia • Activities of daily living • Physical therapy • Vocational therapy • Sensory disturbances • Bowel/bladder control • Occupational therapy • Psychological evaluation

Reprinted with permission from Stroke Framework. *www.jointcommission.org/NR/rdonlyres/27197CD9-702D-4395-89F9-5E46E2F7BBF2/0/D_Section2.pdf.* Accessed December 10, 2007. Copyright © The Joint Commission, 2008.

program (Morrison, 2005). Available on its website is the stroke performance measurement implementation manual, which includes information on background, stroke framework, stroke guidelines (supporting measures), measure information, a data element dictionary, data collection tool, sampling, glossary, and references. It also includes *ICD-9 Clinical Modification* (*ICD-9-CM*) principal diagnosis codes for ischemic stroke, hemorrhagic stroke, and TIA. Because requirements may change annually, it is important to check the Joint Commission website at *www.jointcommission.org* for current requirements. Cost to the hospital for the initial Joint Commission certification can be thousands of dollars.

The framework contains domains for urgent care assessment, acute care hospitalization/treatment, risk factor modification, secondary prevention, education, and rehabilitation. Key measurement areas for these domains are listed in **Table 6-3**. The timeline for certification is shown in **Figure 6-2**.

The 10 Joint Commission–recommended stroke-specific care performance measures are listed in **Table 6-4**. All 10 measures are required for certification as of January 1, 2008. Evidence-based literature to support each performance measure is provided

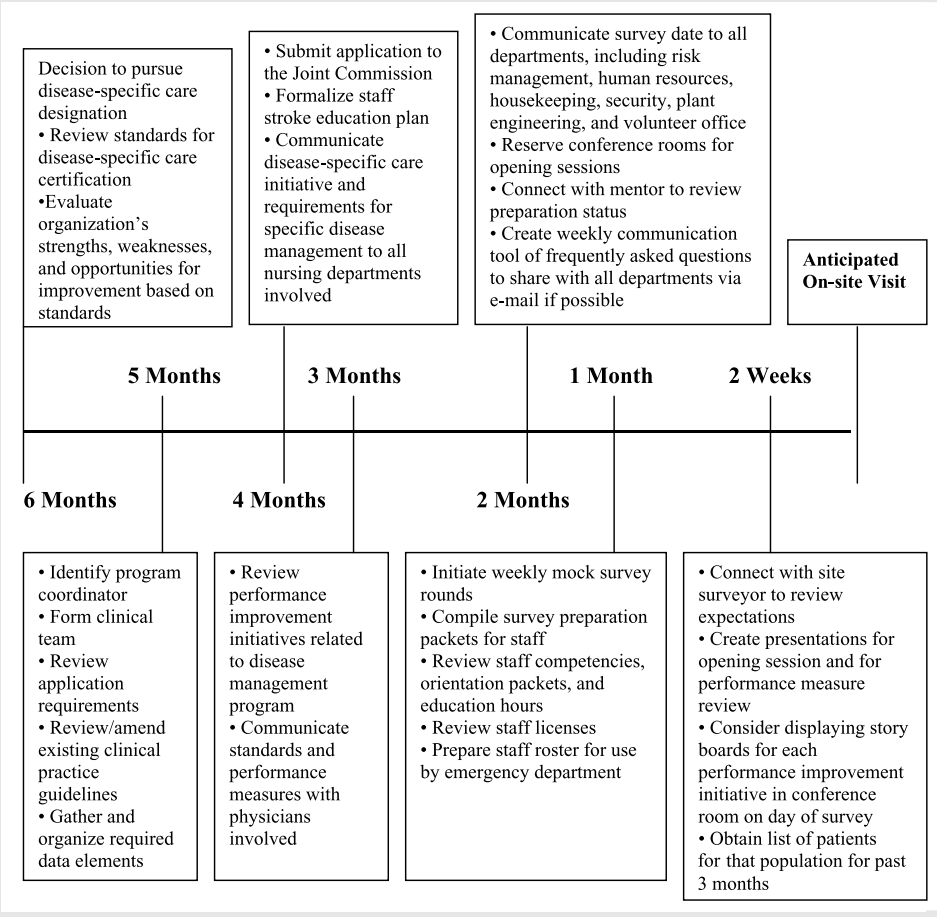

FIGURE 6-2 Disease-specific care certification timeline.

Reprinted with permission from Morrison K. The road to JCAHO disease-specific care certification: a step-by-step process log. Dimens Crit Care Nurs 2005;24(5):221–227.

KEY POINTS

- Data collected allow continuous quality improvement for the hospital—to track each of the performance measures each quarter, to discuss the results with members of the stroke center, and to work on processes to improve the rates of compliance.
- Having regular dialogue and meetings with representatives from various fields can help ensure that care processes and protocols are optimized for the individual stroke center and that the patient's needs are given top priority.

TABLE 6-4 Joint Commission Stroke-Specific Care Performance Measures[a]

- Deep vein thrombosis prophylaxis
- Discharged on antithrombotic therapy
- Patients with atrial fibrillation receiving anticoagulation therapy
- Thrombolytic therapy administered
- Antithrombotic therapy by end of hospital day 2
- Discharged on cholesterol-reducing medication
- Dysphagia screening
- Stroke education
- Smoking cessation/advice/counseling
- Assessed for rehabilitation

[a]Effective January 1, 2008, all 10 measures are required for certification.

Reprinted with permission from Standardized stroke measure set (harmonized measures). *www.jointcommission.org/CertificationPrograms/PrimaryStrokeCenters/standardized_stroke_measure_set.htm.* Accessed December 10, 2007. Copyright © The Joint Commission, 2008.

on the Joint Commission website. These are the new guidelines, and, therefore, this is an iterative process that will require revisions as care standards will evolve. The data elements required to capture for the certification process are also listed and explained in a very straightforward manner. All terms are defined for standardization of data collection and reliability.

The data collected allow continuous quality improvement for the hospital—to track each of the performance measures each quarter, to discuss the results with members of the stroke center, and to work on processes to improve the rates of compliance.

BENEFITS OF BECOMING A PRIMARY STROKE CENTER

By becoming a PSC, an institution can raise its standard of care for acute stroke. PSC designation allows a hospital to develop and implement a protocol for multidisciplinary care of patients with acute and subacute stroke and appropriate use of rt-PA. An example of this is shown in **Figure 6-3**. Expected benefits of becoming a designated stroke center are summarized in **Table 6-5**.

STROKE CENTER PERSONNEL

Stroke is a complex disease that spans several medical and surgical specialties. In order to provide stroke center–level care, it is critical to bring expertise from these different disciplines together to provide synergism in the care of a patient with stroke. Typically, stroke centers would have some level of representation or involvement from the areas of neurology, emergency medicine, radiology/neuroradiology, neurosurgery, internal medicine, physiatry, family practice, vascular surgery, critical care, laboratory medicine/clinical pathology, cardiology, quality assurance, and hospital administration. Having regular dialogue and meetings with representatives from these various fields can help ensure that care processes and protocols are optimized for the individual stroke center and that the patient's needs are given top priority. A ''quarterback''—the director of the stroke center—is needed to facilitate meetings and processes and take overall responsibility for the center's function. Choosing the best person for the job is often a critical factor in the successful operations of the stroke center. Typically this person is a neurologist. Given the current relative lack of subspecialty-boarded vascular neurologists, it is not practical to have fellowship-trained stroke physicians at most hospitals.

The director should expect to commit time to the development and

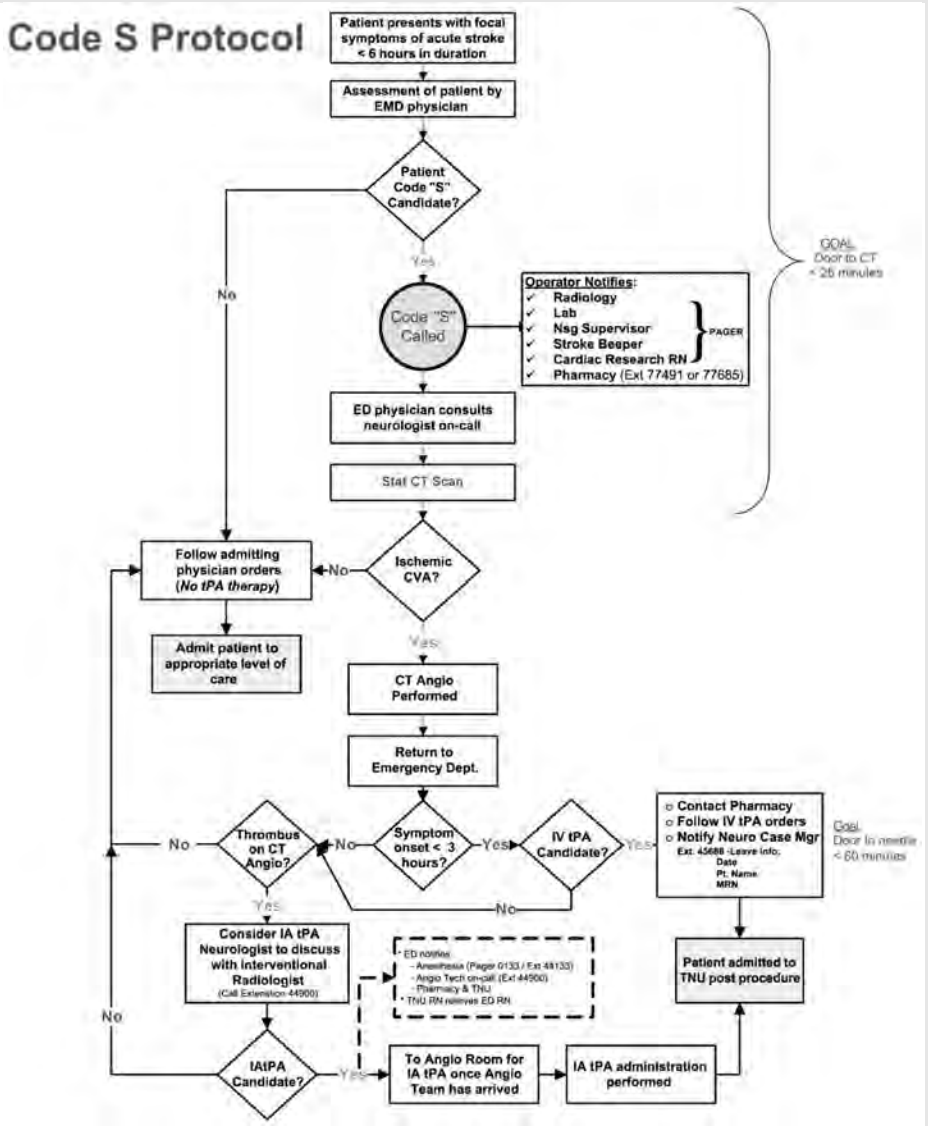

FIGURE 6-3 An acute stroke protocol (''Code S for stroke'').

EMD = emergency medicine department; ED = emergency department; CVA = cerebrovascular accident; tPA = tissue plasminogen activator; IA tPA = intraarterial tissue plasminogen activator; TNU = transitional nursing unit.

Reprinted with permission from Morrison K. The road to JCAHO disease-specific care certification: a step-by-step process log. Dimens Crit Care Nurs 2005;24(5):221–227.

maintenance of the stroke center. Much of the effort to launch the stroke center occurs at the front end of the process. It is optimal, through the support of hospital administration (after they understand the financial benefits of becoming a designated/certified stroke center), to have a stroke center coordinator who works hand in hand with the director and the related disciplines to help conduct quality improvement activities (**Figure 6-4**), insure prospective data capture of all patients with stroke seen or admitted, summarize the data, and help plan the educational activities. Based on stroke volume, this is either a part-time (typically approximately half-time) or full-time position. A skill set for

KEY POINT

- An enlightened hospital administration may even support (and should support) part of the salary/income of the stroke center director for this added and important hospital responsibility.

TABLE 6-5 Expected Benefits of Primary Stroke Centers

- Improved efficiency of patient care
- Fewer peri-stroke complications
- Increased use of acute stroke therapies
- Reduced morbidity and mortality
- Improved long-term outcomes
- Reduced cost to health care system
- Increased patient satisfaction

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both the director and the coordinator should include consensus building with good interpersonal abilities, negotiating savvy, administrative abilities, and excellent clinical skills. An enlightened hospital administration may even support (and should support) part of the salary/income of the stroke center director for this added and important hospital responsibility.

A STEP-BY-STEP GUIDE TO REQUIRED STROKE SERVICES

Commitment to Stroke Services and Their Awareness Within the Hospital and Community

A hospital interested in becoming a stroke center must have an awareness of its acute stroke care abilities and resources and wish to improve them. Preparing a current inventory of relevant services is helpful. Administration within the hospital can help by establishing mechanisms to guide and guarantee working relationships with professional and community groups committed to increasing public awareness of stroke as well as access to acute stroke care. The stroke champion or hospital-appointed professional will be the community liaison and work to improve timely access to acute stroke care for all community members in collaboration with private, public, and voluntary sectors of the

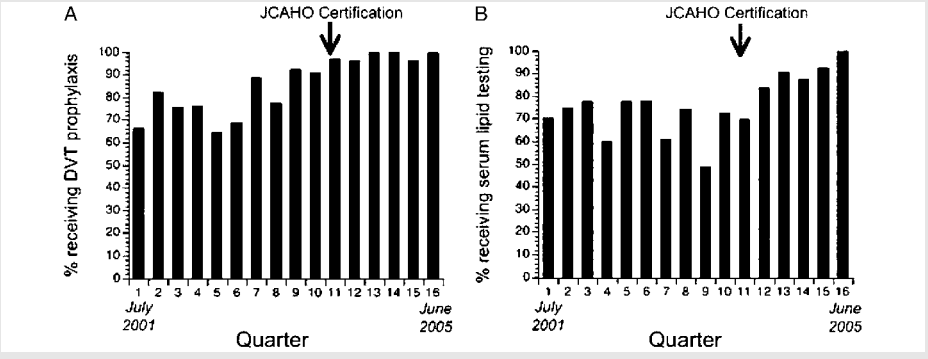

FIGURE 6-4 Examples of measuring Joint Commission (formerly JCAHO) performance measures. Percentage of patients with ischemic stroke receiving (*A*) prophylaxis for deep vein thrombosis (DVT) and (*B*) serum lipid profile testing during admission.

Reprinted with permission from Stradling D, Yu W, Langdorf ML, et al. Stroke care delivery before vs after JCAHO stroke center certification. Neurology 2007;68:469–470. Copyright © 2007, AAN Enterprises Inc. All rights reserved.

community. Twice a year, the hospital stroke center should provide a public education program on stroke risk factors, warning signs, prevention, and acute treatment.

Maximize Optimal Stroke Care

An ongoing and detailed monitoring process is necessary to optimize acute stroke care. This includes time-to-care-process documentation, quality measures, working through barriers, and addressing areas that fall below national benchmark standards. There must be coordination of services with EMS, the ED, nurses, the neurologist, and the departments of radiology, pharmacy, clinical laboratory, rehabilitation, and administration. Ideally, an area should be designated for patients with stroke, which includes designated stroke beds. The leadership of the stroke center should be documented on an ongoing basis, with written acknowledgment by administration, regular stroke team/center meetings, and on-file documentation (curricula vitae) of key stroke center personnel training and expertise. There should be a listing of resources available for the stroke center and a budget.

Maintain Written Care Protocols and Pathways

Written standing orders should be developed based on evidence from the published peer-reviewed medical literature and endorsed by the American Stroke Association/American Heart Association, the AAN, and/or the NIH. This provides and encourages consistency of care and avoids using out-of-date, unproven, and potentially dangerous therapies. These guidelines would include practical approaches to use of diagnostic studies, patient monitoring type and frequency, medications, consultants, and discharge planning. These guidelines should be reviewed and updated annually.

Organize an Acute Stroke Team

A qualified health professional (typically a neurologist, neurosurgeon, or someone with expertise and experience in acute stroke care) should lead the stroke team. At a minimum, a stroke center leader who is board certified or board qualified (as not enough fellowship-trained stroke specialists are available) with special competence in caring for and treating patients with stroke should be designated. In addition, there should be another health care professional, such as a registered nurse, nurse practitioner, or physician's assistant, who is also experienced in caring for patients with stroke. Written documentation of administrative support, staffing, notification plans, response times, and quality improvement procedures and actions taken should be implemented. The acute stroke team should be on call 24 hours a day, 7 days a week, 365 days a year and be available at the bedside within 15 minutes of being notified. A stroke log should be maintained that summarizes all patients with acute stroke that led to stroke team notification, the team's response times, patient diagnosis, treatments, and outcomes.

Integration of Emergency Medical Services

Well-developed communication lines with EMS should be in place. This can be facilitated with a letter of commitment to integrate EMS within the ED of the hospital and can help emphasize the need for rapid patient transport and prehospital stroke scales and assessment. Educational activities for EMS personnel should be provided at least twice a year.

Educate Emergency Department Personnel

Physicians and other health care professionals working in the ED

KEY POINTS

- An ongoing and detailed monitoring process is necessary to optimize acute stroke care.
- The acute stroke team should be on call 24 hours a week, 7 days a week, 365 days a year, and available at the bedside within 15 minutes of being notified. A stroke log should be maintained that summarizes all patients with acute stroke that led to stroke team notification, the team's response times, patient diagnosis, treatments, and outcomes.

KEY POINTS

- The functions of the stroke unit should be documented. These include admission and discharge criteria, care protocols, patient census, and outcomes data.
- Physicians and nurses/staff on the stroke unit must receive a minimum of 8 hours of continuing medical education or its equivalent credit annually in the area of care of patients with cerebrovascular disease.

should receive formal education on all aspects of acute stroke (ischemic and hemorrhagic)—history, examination, NIH Stroke Scale score, diagnostic studies, treatment (specifically including rt-PA), supportive care, monitoring, and outcome. They should also be updated regularly to ensure familiarity with procedures for communicating with EMS and activating the stroke team. ED personnel should attend CME programs on stroke at least twice a year.

Ensure Rapid Access to Neuroimaging (Typically Head CT Scanning)

There should be a written agreement and understanding between the stroke center leader/director and the chief of radiology that documents rapid access to head CT scanning and its interpretation for acute stroke patients 24 hours a day, 7 days a week, 365 days a year. Head CT (or MRI) should be performed within 20 minutes of being ordered and interpreted within 20 minutes of the study's completion. This can be performed, as necessary, using telemedicine (teleradiology). Documentation, such as a logbook, should be provided for all stroke CT requests and interpretations to assess compliance with these guidelines.

Availability of Laboratory Services

A written agreement and understanding should be established between the stroke center leader/director and the chief of laboratory services that documents rapid access (within 45 minutes of being ordered) to specific, stroke-related (rt-PA protocol required) laboratory studies 24 hours a day, 7 days a week, 365 days a year. A logbook should be provided for documentation of all acute stroke laboratory studies to assess compliance with these guidelines.

Stroke Unit/Designated Beds Availability

A designated unit should be available for patients with stroke beyond the acute treatment period, either within the stroke center or at another site. These arrangements should be prespecified and written. The functions of the stroke unit should be documented. These include admission and discharge criteria, care protocols, patient census, and outcomes data. Physicians, nurses, and staff on the stroke unit team must receive a minimum of 8 hours of CME or its equivalent credit annually in the area of care of patients with cerebrovascular disease. The stroke unit should be equipped with necessary tools and technology to properly care for patients with stroke who are medically stable. These include written care protocols and capability to continuously and noninvasively monitor blood pressure and cardiac rhythm. This may be accomplished by locating the acute stroke designated beds within an intensive care unit.

Focus on Secondary Stroke Prevention

A key part of the stroke center is the coordinated multidisciplinary approach to prevent recurrent stroke and vascular events. Standardized prewritten orders should be available to ensure stroke mechanism-based prevention measures, treatments, and risk factor modification. Prewritten orders to assess/monitor and address potential complications are also required.

Focus on Patient/Family Education and Support

Standing orders to address education requirements should be available for all patients and their families. Information should address definition of a stroke, types of stroke, prognosis, treatment options, complications, risk

factors and their modification, post-stroke support services (including stroke clubs), and warning signs.

Discharge Planning

Each patient with acute stroke admitted to the stroke center should have a clear plan for discharge and placement after acute hospitalization. There should be a systematic identification of potential candidates for rehabilitation as well as follow-up for continuity of care with a physician knowledgeable about stroke.

Continuous Quality Improvement for Stroke Outcomes

The stroke center must have established outcome measures that are time specific and quantifiable. At least annual comparison of stroke outcomes at the stroke center with established national benchmarks and comparator hospitals should be done. The stroke center director ought to maintain a stroke database/data system/registry that can track the number and type of stroke patients seen, their treatments, time to key processes, and the quality improvement indicators. Regular meetings should be held (at least 2 to 3 times a year and preferably quarterly) involving the stroke team and personnel from quality assurance. Data should be reviewed and critiqued; bad outcomes and indicators below national standards should be discussed with the focus on improving current systems of care. The stroke center director should maintain documentation of steps taken to improve outcomes, costs, reduce length of stay, increase admissions, and establish uniform practice standards among physicians caring for patients with stroke. The stroke center priorities will be based on this information and the need to provide continuity of professional and public education. Finally, a strategic plan for the stroke center should be formulated by the stroke center director and stroke team. This will assess the population's need for acute stroke care and the stroke center's capability to provide for these needs. Ongoing internal and external monitoring should be done with adjustments made as needed (Tilley et al, 1997). **Figure 6-5** provides an example of tracking t-PA use before and during a pilot phase and after developing a stroke team within a stroke center.

Once a stroke center is up and running, there are ongoing maintenance costs to maintain the high quality of care (**Table 6-6**).

STROKE EDUCATION

The need to educate both professionals and the public about stroke is great, considering that fewer than 5% of all patients with strokes receive the only USFDA-approved and proven therapy for acute ischemic stroke. Key areas include providing information

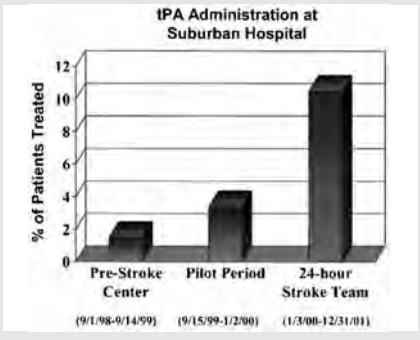

FIGURE 6-5 Percentage of patients treated with recombinant tissue-type plasminogen activator related to the establishment of a primary stroke center.

t-PA = tissue plasminogen activator.

Reprinted with permission from Lattimore SU, Chalela J, Davis L, et al. Impact of establishing a primary stroke center at a community hospital on the use of thrombolytic therapy: the NINDS Suburban Hospital Stroke Center experience. Stroke 2003;34(6):e55–e57.

KEY POINTS

- The stroke center director should maintain documentation of steps taken to improve outcomes, reduce costs, reduce length of stay, increase admissions, and establish uniform practice standards among physicians caring for patients with stroke.
- The need to educate both professionals and the public about stroke is great, considering that fewer than 5% of all patients with strokes receive the only USFDA-approved and proven therapy for acute ischemic stroke.

TABLE 6-6 Annual Cost Estimates for Primary Stroke Centers

Cost Item	Amount[a]
Acute stroke team	$5000 to $20,000
Stroke unit[b]	$0 to $120,000
Radiology technician coverage	$0 to $50,000
Physician leader	$0 to $20,000
Staff education support	$1000 to $5000
Public educational programs	$2000 to $10,000
Marketing	$0 to $20,000

[a]These cost estimates vary based on the current staffing levels, programmatic support, reimbursement policies, and infrastructure at a specific hospital. Hospitals with ongoing stroke programs may not have to expend additional monies in these areas.

[b]Costs for the stroke unit are based on additional staffing needs and do not include the costs of new infrastructure (ie, room renovations, telemetry equipment) needed to build a new unit. Staffing costs will vary depending on current staffing levels, duties, and coverage at specific hospitals.

about why stroke is a major medical emergency and that stroke is common, serious, and expensive. The need to activate 911 is a crucial public message. The data from **Table 6-7** support the need for professional education.

The Joint Commission requires that the core stroke team have 8 hours of continuing stroke education annually. Each team is defined by the individual hospital. The core team is typically composed of staff responsible for oversight of the stroke program and protocols. The 8 hours of continuing education can be accomplished through various methods, such as grand rounds, seminars or conferences, internet-based learning, and literature review. Certified medical education (CME) is not specifically required by the Joint Commission. The methods used for continuing education may not have CME attached but need to be specific to stroke.

As stated on the Joint Commission website, the American Stroke Association expert panel would recommend that this team have 8 hours of continuing education units from conferences that provide updates on acute stroke care. A minimum of 80% of the ED staff is required to be knowledgeable about the organization's acute stroke protocol. The staff that provides direct care to the patient with stroke should receive stroke education, but 8 hours is not required. This would include staff from the critical care, neurology, and step-down units or wherever the stroke patient may receive care in the organization. Nurses on nonstroke units, where patients with stroke are not routinely provided care, and ancillary staff, such as housekeeping and dietary, are supposed to understand the signs and symptoms of stroke. In addition, they need to understand how to activate the organization's emergency response team.

Specific content typically addressed at conferences geared for professional stroke education updates include

TABLE 6-7 Results of Opinion Questions About Stroke Centers Provided by Specialty

Opinion	Results[a] GN	SCCN	EP	NS	NSA	All
Felt there is a need for stroke centers	82	77	58	88	98	79
Expressed desire for their primary hospital to be designated as a primary stroke center	79	80	72	86	90	81
Expressed desire for their primary hospital to be designated as a comprehensive stroke center	74	71	59	89	94	76
Felt EMS diversion of patients with acute stroke to designated stroke centers is a good idea	74	68	50	84	91	72
Felt that national regulations should be developed to standardize EMS	61	67	50	66	90	64
Felt that the benefit of IV t-PA outweighs the risk	76	80	53	73	95	74
Felt that the level of reimbursement influences IV t-PA administration decisions	3	5	1	2	6	3

[a]Numbers are percentages.

GN = general neurologists; SCCN = stroke and critical care neurologists; EP = emergency department physicians; NS = neurosurgeons; NSA = National Stroke Association Stroke Center Network members; EMS = emergency medical services; t-PA = tissue plasminogen activator.

Data from Kidwell CS, Shephard T, Tonn S, et al. Establishment of primary stroke centers: a survey of physician attitudes and hospital resources. Neurology 2003;60(9):1452–1456.

management of both hemorrhagic and ischemic acute stroke, management of acute TIAs, pre–hospital care of acute stroke, updates on stroke certification and designation processes (Joint Commission and state based), stroke pathogenesis and etiology, brain and vascular imaging, treatment (the spectrum of acute options), risk factor identification and management, ongoing relevant clinical trials, rehabilitation/recovery/repair and restoration, and nursing issues.

DEVELOPING A LINK TO A COMPREHENSIVE STROKE CENTER

While focusing at first on primary stroke centers, the Brain Attack Coalition also mentioned the need for establishing comprehensive stroke centers (CSCs). PSCs would provide emergency care and stabilize patients, and the CSCs would provide complete care for the most complex stroke cases. Everything that is needed for stroke care would be available at the CSC site, and patients could be transferred from a PSC to the nearest CSC if deemed necessary. CSC certification brings stroke care to an even higher level, and recommendations were established in 2005 in order to make this next step possible (Mohammad et al, 2006). Once enough CSCs are established, PSCs need to develop a link with the closest CSC so as to develop regional networks for acute stroke care, in which several PSCs would branch off each CSC. These

networks would then allow for fast patient transfers and make it easier to enroll patients in clinical trials, which are needed to develop new, more effective treatments for stroke. Linking a PSC to a CSC allows ongoing support and development of relationships that can only improve patient care.

REFERENCES

Alberts MJ, Hademenos G, Latchaw RE, et al. Recommendations for the establishment of primary stroke centers. Brain Attack Coalition. JAMA 2000;283(23):3102–3109.

Arora S, Broderick JP, Frankel M, et al. Acute stroke care in the US: results from 4 pilot prototypes of the Paul Coverdell National Acute Stroke Registry [published erratum appears in Stroke, 2005,36(8):1820]. Stroke 2005;36(6): 1232–1240.

Bambauer KZ, Johnston SC, Bambauer DE, Zivin JA. Reasons why few patients with acute stroke receive tissue plasminogen activator. Arch Neurol 2006;63(5):661–664.

Burgin WS, Staub L, Chan W, et al. Acute stroke care in non-urban emergency departments. Neurology 2001;57(11):2006–2012.

Demaerschalk BM, Durocher DL. How diagnosis-related group 559 will change the US Medicare cost reimbursement ratio for stroke centers. Stroke 2007;38(4):1309–1312.

Demaerschalk BM, Yip TR. Economic benefit of increasing utilization of intravenous tissue plasminogen activator for acute ischemic stroke in the United States. Stroke 2005;36(11):2500–2503.

Fagan SC, Morgenstern LB, Pettita A, et al. Cost-effectiveness of tissue plasminogen activator for ischemic stroke. NINDS rt-PA. Stroke Study Group. Neurology 1998;50(4):883–900.

Gomez C. Time is brain. J Stroke Cerebrovasc Dis 1993;3:1–2.

Joint Commission. Primary stroke center certification. *www.jointcommission.org/CertificationPrograms/PrimaryStrokeCenters/*. Accessed: December 10, 2007.

Kidwell CS, Shephard T, Tonn S, et al. Establishment of primary stroke centers: a survey of physician attitudes and hospital resources. Neurology 2003;60(9): 1452–1456.

Kleindorfer D, Hill MD, Woo D, et al. A description of Canadian and United States physician reimbursement for thrombolytic therapy administration in acute ischemic stroke. Stroke 2005;36(3):682–687.

Kleindorfer D, Khoury J, Alwell K, et al. rt-PA use in a population-based study: the post-FDA approval era. Stroke 2003;34(1):283.

Kleindorfer D, Kissela B, Schneider A, et al. Eligibility for recombinant tissue plasminogen activator in acute ischemic stroke: a population-based study. Stroke 2004;35(2):e27–e29.

Kwiatkowski TG, Libman RB, Frankel M, et al. Effects of tissue plasminogen activator for acute ischemic stroke at one year. National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study Group. N Engl J Med 1999;340(23):1781–1787.

Lattimore SU, Chalela J, Davis L et al. Impact of establishing a primary stroke center at a community hospital on the use of thrombolytic therapy: the NINDS Suburban Hospital Stroke Center experience. Stroke 2003;34(6):55–57.

Mohammad YM, Divani AA, Jradi H, et al. Primary stroke center: basic components and recommendations. South Med J 2006;99(7):749–752.

Morrison K. The road to JCAHO disease-specific care certification: a step-by-step process log. Dimens Crit Care Nurs 2005;24(5):221–227.

National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group: Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333(24):1581–1587.

Saver JL. Time is brain—quantified. Stroke 2006;37(1):263–266.

Tilley BC, Lyden PD, Brott TG, et al. Total quality improvement method for reduction of delays between emergency department admission and treatment of acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Arch Neurol 1997;54(12):1466–1474.

ADDITIONAL READINGS AND RESOURCES

Adams R, Acker J, Alberts M, et al. Advisory Working Group on Stroke Center Identification Options of the American Stroke Association. Recommendations for improving the quality of care through stroke centers and systems: an examination of stroke center identification options: multidisciplinary consensus recommendations from the Advisory Working Group on Stroke Center Identification Options of the American Stroke Association. Stroke 2002;33(1):el–7.

American Academy of Neurology. Coding for t-PA infusion-related physician work. *www.aan.com/globals/axon/assets/2858.pdf*; *www.aan.com/news/?event=read&article_id=5264&page=243.33.33*. Accessed August 25, 2008.

Douglas VC, Tong DC, Gillum LA, et al. Do the Brain Attack Coalition's criteria for stroke centers improve care for ischemic stroke? Neurology 2005;64(3):422–427.

Hacke W, Donnan G, Fieshci C, et al. ATLANTIS Trial Investigators, ECASS Trial Investigators, NINDS rt-PA Study Group Investigators. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA Stroke trials. Lancet 2004;363(9411):768–774.

Levine SR, Gorman M. ''Telestroke'': the application of telemedicine for stroke. Stroke 1999:30(2):464–469.

Program Capacity Assessment Criteria, American Stroke Association. Schneider SM, Goldstein LB, Adams JG, et al. Incentives for enhancing stroke care. National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group. A systems approach to immediate evaluation and management of hyperacute stroke: experience at eight centers and implications for community practice and patient care. Stroke 1997;28(8):1530–1540.

National Institute of Neurological Disorders and Stroke, National Institutes of Health Web site. *www.ninds.nih.gov/news_and_events/proceedings/stroke_2002/acute_stroke_incentives.htm*. Updated May 29, 2007. Accessed December 10, 2007.

Stradling D, Yu W, Langdorf ML, et al. Stroke care delivery before vs after JCAHO stroke center certification. Neurology 2007;68(6):469–470.

''HOW TO'' GUIDE FOR CLINICIANS INTERESTED IN BECOMING INVOLVED IN CLINICAL STROKE RESEARCH

Steven R. Levine, David Adamowicz, Karen C. Johnston

ABSTRACT

Clinical stroke research is typically performed within the domain of large academic medical centers led by stroke specialists generally well versed in clinical trial methodology and performance. Practitioners who see and treat patients with stroke on a regular basis, either as inpatients acutely or as outpatients after the acute hospitalization, have the opportunity to help advance stroke care by testing the same new and promising therapies that are being employed at academic medical centers. This chapter provides an overview of clinical trial structure and implementation that we hope will provide impetus to the practitioner to consider becoming involved in stroke clinical trials. The benefits to practitioners include providing the same promising treatments that patients receive at tertiary care stroke centers, greater patient satisfaction in knowing they are getting state-of-the-art care, enhanced referral patterns, and financial remuneration, among others. Topics covered include resources needed, relationship to academic medical centers, ethical and institutional review board issues, patient perspective, budget, recruitment, informed consent, data collection and management, safety, outcome measures, and lessons from other diseases.

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INTRODUCTION

Clinical research allows discovery of new knowledge and improved patient care that is immediately transferable to patients. In the setting of clinical equipoise when the stroke community does not know which treatment is better, randomized clinical trials (RCTs) are conducted as the criterion standard for evaluating treatments to determine optimal care. RCTs are essential in such a setting when the preferred

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Levine discusses the unlabeled use of experimental therapies for stroke. Dr Adamowicz has nothing to disclose. Dr Johnston discusses the unlabeled use of investigational therapies.

KEY POINTS

- Improved evidence-based stroke care can only emerge as a result of carefully conducted clinical research.
- Practice-based research participation may speed enrollment into clinical trials so that answers can be forthcoming in a more timely manner.

treatment is unknown. Improved evidence-based stroke care can only emerge as a result of carefully conducted clinical research, primarily from RCTs, although many other types of clinical research exist. As rapid enrollment facilitates efficient answers to important clinical questions, a commitment to clinical research by both academic and practicing physicians would improve stroke patient care (**Table 7-1**). Additionally, the availability of clinical research options offers the patients an additional treatment option that may improve their outlook, as well as their outcome, after stroke or in the prevention of stroke. This chapter will review basic information about conducting clinical research (with a focus on RCTs), the available resources, and the potential benefits and potential costs of participation.

An evaluation of 28 National Institute of Neurological Disorders and Stroke (NINDS)-funded RCTs conducted over 2 decades from 1980 to 2000 determined that the cost to taxpayers was $335 million, but the net benefit to society over a 10-year period was $15.2 billion. An estimated 470,000 additional quality-adjusted life years were saved as a result of these trials (Johnston et al, 2006).

Research performed in the private practice setting allows access to an unselected heterogeneous patient population (versus selection biases inherent to tertiary referral centers). Further, practice-based research participation may speed enrollment into clinical trials so that answers can be forthcoming in a more timely manner.

ASPECTS TO CONSIDER

A private practitioner can become involved in clinical trials in several ways. The most direct method is to become an investigator. Many physicians list time commitment as a major barrier to involvement (Ross et al, 1999). However, with careful planning, in addition to an organized and well-trained supporting staff, the time commitment can be kept to the minimum necessary.

TABLE 7-1 Potential Benefits of Participating in Clinical Trials

▶ Networking with other clinicians interested in the same problem or disease
▶ Becoming an active member of the clinical research community
▶ Helping answer important questions about the causes of disease
▶ Being able to offer patients state-of-the-art/cutting-edge treatments that are often only available at large, academic medical centers
▶ Advancing the field and helping to create new knowledge
▶ Improving generalizability of research results
▶ Providing faster answers to important clinical questions
▶ Receiving named participation in publications and presentations (good advertising for the practice)
▶ Enhancing referral patterns from clinicians in neighboring areas who are not participating in trials
▶ Bringing supplemental income into the practice

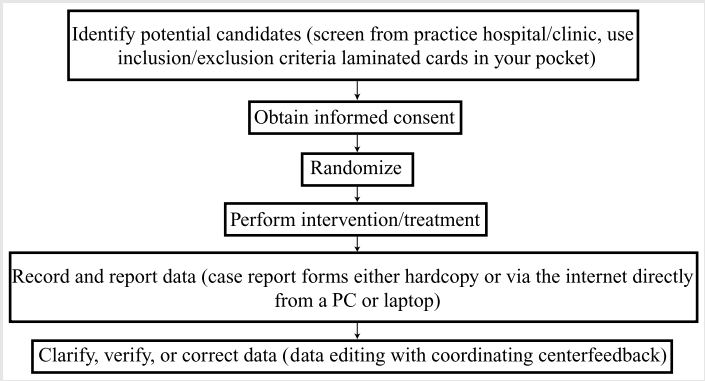

FIGURE 7-1 General steps in conduct of randomized controlled trials.

Adapted with permission from Lader EW, Cannon CP, Ohman EM, et al. The clinician as investigator: participating in clinical trials in the practice setting. Circulation 2004;109(21):2672–2679.

KEY POINT

- The first requirement for becoming an investigator is motivation.

The first requirement for becoming an investigator is motivation. A motivated investigator will positively affect all those working on the project, which will help the trial move along smoothly. The investigator also needs practical experience in the target area (eg, acute stroke and/or stroke prevention), as well as knowledge of the RCT study design and, if so predisposed, statistical methods. **Figure 7-1** outlines the basic steps involved in conducting a clinical trial. Certain characteristic features of trials can be learned along the way through organizational meetings, a manual of operations, Web sites, and telephone assistance, among other things. Certain universities and teaching hospitals as well as private and commercial research organizations offer courses in conducting clinical trials, which may also be useful for getting started.

Before starting, the investigator must consider various aspects of the trial (Chen and Worrall, 2006a; Chen and Worrall, 2006b), including what stage of development the drug is in, what kind of doses given, and what ethical issues involved (**Figure 7-2**). It is also important to know whether a placebo arm is used and whether the trial is double-blinded, which reduces the possibility of bias.

If it is a phase 3 RCT, the appropriate in vitro and in vivo work should have been done beforehand. Unfortunately, this is not always the case because of

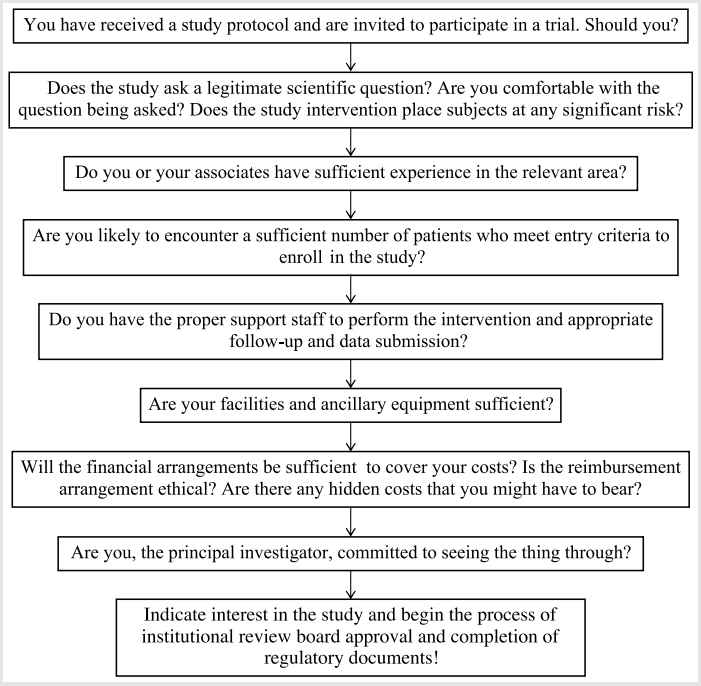

FIGURE 7-2 How to decide whether to participate in a clinical trial.

Adapted with permission from Lader EW, Cannon CP, Ohman EM, et al. The clinician as investigator: participating in clinical trials in the practice setting. Circulation 2004;109(21):2672–2679.

KEY POINTS

- Evidence from nonurban emergency departments indicates that acute stroke care is generally not performed according to published guidelines or clinical trial results (evidence-based medicine).
- A research coordinator (preferably one with previous clinical trial experience) can be helpful in greatly limiting the investigator's time commitment to the trial.
- Private practitioners have a plethora of resources at their disposal to help them become involved in clinical trials for stroke.

competitive time pressure from the sponsoring agencies, such as pharmaceutical companies (Chappell, 2001).

Many sources are available to help private practitioners identify suitable trials that are looking for investigators (discussed later in this chapter). Once having become investigators, they can go a step farther by becoming part of writing groups, helping to report the results of the trials in which they have participated. Another way for physicians to become involved in clinical trials, although less direct, is simply to refer patients to trials that are recruiting subjects. These trials could be going on in nearby hospitals or research centers. Because private practitioners see so many clinical cases, such a small step would provide great support to those conducting trials.

Evidence from nonurban emergency departments (Burgin et al, 2001) indicates that acute stroke care is generally not performed according to published guidelines or clinical trial results (evidence-based medicine). This suggests that simply by having the practitioner enroll eligible patients in acute stroke trials, the quality and level of acute stroke care would be optimized with the additional added benefit of avoiding potential malpractice allegations.

RESOURCES NEEDED

Additional personnel are recommended when adding clinical trials to a private practice. A research coordinator (preferably one with previous clinical trial experience) can be helpful in greatly limiting the investigator's time commitment to the trial. The coordinator would typically be a nurse, nurse practitioner, physician's assistant, or trained individual with a medical background (Lader et al, 2004). The coordinator would be in charge of the day-to-day activities relating to the trial, including overseeing trial logistics such as training the other staff involved, making sure that all the equipment and supplies necessary are available, and following up regularly with the patients. The coordinator would also track the course of the trial. There could be a need for more nurses in order to cut down on waiting times. It can also be useful to hire research assistants who would collect and process the data. All staff involved should be familiar with the design of the trial and the specific aspect of the protocol assigned for which they are responsible. If a telemedicine unit is used, additional technical staff may be necessary to operate the unit. The number of new personnel that are needed will depend on the size of the trial and the number of concurrent trials going on in the office or hospital.

Private practitioners have a plethora of resources at their disposal to help them become involved in clinical trials for stroke. Many government-sponsored Web sites as well as university Web sites are looking for investigators for clinical trials. Large academic institutions are often involved in multiple multicenter trials that are sponsored by the government or by pharmaceutical companies, and private practitioners can participate with their institution as one of the study sites (**Figure 7-3**). The Stroke Trial Registry (*www.strokecenter.org/trials*) is an extensive online database of ongoing and completed stroke trials. The NIH Web site (*www.nih.gov*) also has a listing of clinical trials for stroke. In addition to its listings, the NIH has created an online community-based network dedicated to clinical research through its NIH Roadmap for Medical Research Initiative (*nihroadmap.nih.gov*) so that investigators can share resources (Lader et al, 2004). The NINDS also has a similar network, which is called the NINDS Clinical Research Collaboration (*nindscrc.org* or *www.ninds.nih.gov/funding/research/clinical_research/crc.htm*).

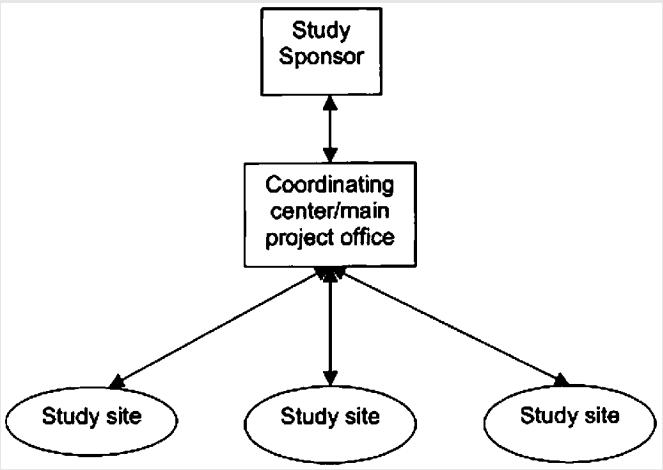

FIGURE 7-3 Simplified organizational structure of clinical trial.

Reprinted with permission from Lader EW, Cannon CP, Ohman EM, et al. The clinician as investigator: participating in clinical trials in the practice setting. Circulation 2004;109(21):2672–2679.

The NIH-funded Clinical Research Collaboration project facilitates the inclusion of private doctors to participate at various levels (highly flexible) in clinical research activities. This is a great resource, and we strongly encourage the reader to access the Web site and learn more. An extremely helpful researcher's toolkit walks a clinician through the process. Practitioners can participate in registries and all phases of clinical trials, including RCTs, or they can just identify patients from their practice and send them to nearby enrolling sites. Alternatively, they can participate in full enrollment and follow-up through final outcome measures.

For government-sponsored trials, one can sort listings on the Web site *clinicaltrials.gov* by condition and include only the ones relating to stroke.

A ''site visit'' or ''field trip'' to another regional practice involved in clinical research is a good way to gain insight into the advantages and challenges that accompany becoming involved in clinical research.

Regular, optimally weekly, meetings of the clinical trial personnel and involved staff is extremely useful to review trial progress, recruitment issues, and unexpected challenges and barriers.

RELATIONSHIP TO ACADEMIC CENTERS

For the successful operation of a clinical trial performed in the private practice setting, working with a nearby or regional academic medical center is very useful. It can help with developing the study design and protocol, assisting with institutional review board (IRB) and Health Insurance Portability and Accountability Act (HIPAA) issues and approval, as well as the logistics of the trial, including staffing, resources, and equipment requirements. For example, an academic center can provide quick responses to tests that cannot be done at the private practice itself. In addition, it can review the ethics of the trial and help with staff training. For trials that involve acute stroke treatments in which the subjects usually have to be enrolled within a certain narrow time window after symptom onset, this training is necessary in order to minimize delays in the chain from time of enrollment to the administration of treatment (Lyden et al, 1994).

KEY POINTS

- The NIH-funded Clinical Research Collaboration project facilitates the inclusion of private doctors to participate at various levels (highly flexible) in clinical research activities.
- A site visit or field trip to another regional practice involved in clinical research is a good way to gain insight into the advantages and challenges that accompany involvement in clinical research.

KEY POINT

- Investigators must understand their moral and legal duties throughout the trial, as well as the regulations that govern all kinds of human research.

ETHICAL AND INSTITUTIONAL REVIEW BOARD ISSUES

Before being able to recruit patients for a clinical trial, the investigator must work with an IRB. The IRB will determine whether it feels the trial protocol is ethical and might require certain changes to be made. The procedure for obtaining consent is heavily scrutinized, especially in the case where patients cannot give consent themselves because of their medical condition. The IRB also makes sure that there are no conflicts of interest, such as the primary investigator having a stake in the company producing the drug about to be investigated (eg, stock or other investments). If any financial incentives are involved, they must be disclosed to the IRB for review.

Investigators must understand the moral and legal duties to which they are obligated throughout the trial, as well as the regulations that govern all kinds of human research (**Figure 7-4**). They must also comply with HIPAA, which was designed to protect patient privacy (Lader et al, 2004). When private practitioners do not have direct access to an IRB through their own institution, they can work with a regional IRB or one from a nearby teaching hospital.

The practitioner must be aware of patients' "therapeutic misconceptions" that exist about clinical trials. Clinical practice is not the same as clinical research. The primary goal of clinical practice includes providing the best established care for each patient. The primary goal of clinical research is to test the safety and/or efficacy of a new and promising treatment in a scientific manner. This concept must be understood by the practitioner before entering the clinical trials arena and must also be accurately conveyed to the patient for whom a clinical trial is being considered. Patients should not be misled about the real or perceived benefits of participating in a clinical trial that would go above and beyond their usual care.

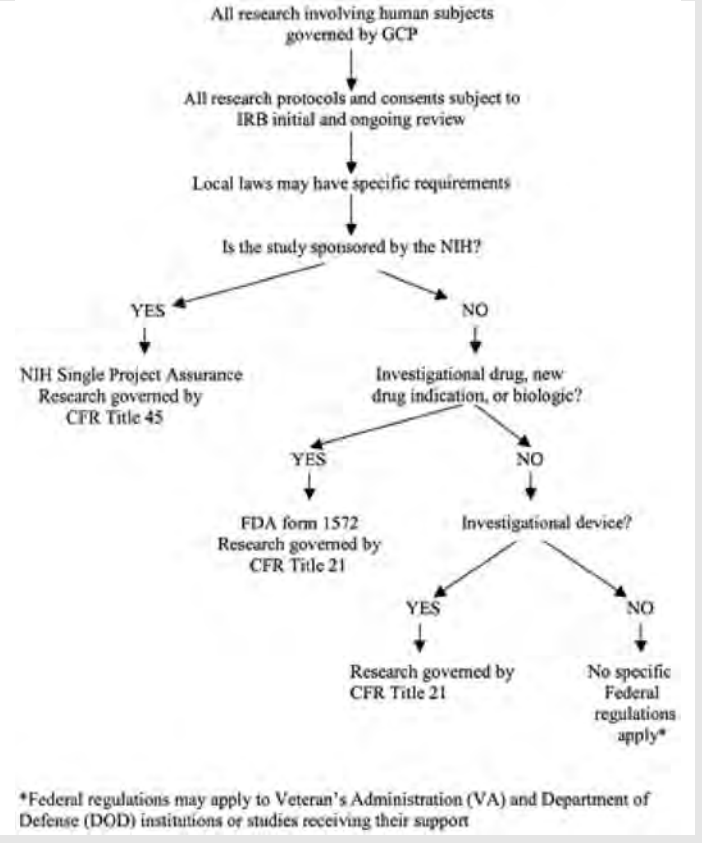

FIGURE 7-4 Overview of regulations governing human research.

GCP = good clinical practice; IRB = institutional review board; CFR = Code of Federal Regulations; NIH = National Institutes of Health; FDA = US Food and Drug Administration.

Reprinted with permission from Lader EW, Cannon CP, Ohman EM, et al. The clinician as investigator: participating in clinical trials in the practice setting. Circulation 2004;109(21): 2672–2679.

PATIENT PERSPECTIVE

Patients enrolling in clinical trials should not regret doing so and, in the ideal world, should be made to feel eager to participate to receive cutting-edge care and a chance at a treatment that is most promising for a serious disease. Unfortunately, many patients feel that they are being asked to be "guinea pigs"—to be the one to test a treatment that has not been

established to be safe or useful. Some degree of distrust exists, in part because prior ethical issues in clinical trials have been highly publicized. Specifically, the Tuskegee Experiment was one of the United States' most historical and grievous breaches of clinical trial ethics. The study involved 399 African American men with syphilis who were deliberately not treated so investigators could study how the disease damages the body. A study like that certainly could not be conducted today with the sensitized and watchful eyes of IRBs.

There should be no cost for the patient when participating in clinical trials, even for follow-up to a study (Lader et al, 2004). Travel fees, as well as any other expenses stemming from the trial, should be reimbursed. The health of the patient should be a primary concern, and the trial should be able to be stopped at any time in the event of serious adverse effects. Furthermore, patients should have the right to stop participating in a trial at their request. A change in the doctor-patient relationship has been cited as a barrier to participation in clinical trials (Ross et al, 1999), but using the guidelines above, trust can be maintained in the relationship, and patient satisfaction can be ensured.

Patients should also be educated on the different phases of clinical trials, such as phase 1, which is typically conducted for safety and feasibility. Most phase 2 studies are RCTs. Often these studies are double-blinded—neither the patients nor the researchers know who is getting the experimental drug. Comparative information about the relative safety of the new drug and its effectiveness can be obtained. Only about one-third of experimental drugs successfully complete both phase 1 and phase 2 studies. Phase 3 RCTs are typically conducted to obtain definitive data on a treatment's benefits and risks based on promising results from phase 2 studies. Phase 4 trials are post–US Food and Drug Administration (USFDA) approval studies investigating how the treatment is working in ''the real world''—safety and efficacy.

A useful Web site, *www.sephmersciences.com/Test.html*, provides information (videos) about the conduct of clinical trials and strategies to help patients make decisions and allows investigators to gain insight into the ethics required in conducting clinical trials. The USFDA also has a Web site, *www.fda.gov/oc/gcp/*, that discusses good clinical practice in USFDA-regulated clinical trials. CenterWatch provides a clinical trials listing service, *www.centerwatch.com/patient/backgrnd.html*.

For such devastating diseases as ALS and glioblastoma multiforme for which there is no proven beneficial treatment, clinical research (ie enrollment into an RCT) may be the only hopeful option for patients. For stroke, some treatments exist, but many patients have few options without research. Clinical research provides hope and choices, and therefore control, as well as improved care.

BUDGETARY ISSUES

Before beginning a clinical trial, a budget must be negotiated among the investigators, coordinating center, and sponsor. Prior to signing any contracts with the sponsoring agency, it is very important for first-time and inexperienced investigators to discuss and review the budgets with more experienced researchers. This will ensure that the costs associated with the trial conduct are not underestimated because doing so would then impose financial burden on the practice.

Individuals working in the trial should be paid in accordance with the extent to which they are involved in the conduct of the trial. The cost for

KEY POINTS

- Patients enrolling in clinical trials should not regret doing so and, in the ideal world, should be made to feel eager to participate to receive cutting-edge care and a chance at a treatment that is most promising for a serious disease.
- Although some treatments are available for stroke, many patients have few options without research. Clinical research provides hope and choices, and therefore control, as well as improved care.

KEY POINT

- Based on the agreed-upon amount for the investigator's and coordinator's time and effort, ample opportunity exists to craft a budget that could allow monies into the clinical practice from patient enrollment.

supporting the trial should include, in addition to remuneration for the staff (investigators, coordinators), the cost of additional equipment if necessary, costs for laboratory and diagnostic testing (that is not part of routine clinical care), and training and advertising costs. Typically, hospitals and clinics offer a discounted cost for research-related diagnostic testing.

In the case of laboratory tests, such as those used for screening purposes, not being covered in the budget, the investigator can often negotiate a discounted rate with a laboratory or local hospital. All costs should be included in the budget whenever possible so that conducting the trial is not a losing financial proposition. Other costs that are not covered in the budget can sometimes be paid through a research fund, which has been established using the surplus funds from earlier trials. Based on the agreed-upon amount for the investigator's and coordinator's time and effort, ample opportunity exists to craft a budget that could allow monies into the clinical practice from patient enrollment. This could then offset clinical care costs for uninsured or underinsured patients. The institution or practice group participating may also receive indirect financial benefits, such as added prestige, which should be considered when drafting a budget (Lader et al, 2004).

RECRUITMENT ISSUES

Recruiting subjects for clinical trials is not as easy as it may seem when dealing with stroke patients. Issues regarding consent can be troublesome, for instance when the patient is unable to give consent. This could be due to loss of consciousness or aphasia, for example. Surrogate consent is often obtained for participation in acute stroke clinical trials. The closest legal relative or spouse is provided with the information about the patient's condition, prognosis, and treatment options and reads and discusses the informed consent document with the study personnel. This surrogate makes the final determination about whether the patient should be enrolled in the trial.

Two crucial factors need to be considered when recruiting: (1) the number of subjects needed and (2) the duration of time it will take to enroll them (Elkins et al, 2006). Efficiency in recruiting will be influenced by the organization of the trial, as well as the stringency of entry criteria (ie, inclusion and exclusion criteria). Some trials will require a very specific subset of patients with stroke, such as only those patients with lacunar infarcts or patients with acute stroke associated with hyperglycemia. Therefore, it could take a long time to gather a body of data that is large enough for meaningful analysis and definitive results. In some cases, a compromise has to be made by relaxing the entry criteria—for example expanding the eligibility from lacunar infarcts alone to all subcortical strokes. However, in doing so, the trial's integrity cannot be jeopardized. Many acute stroke trials testing neuroprotective drugs have made the mistake of including subjects with lacunar infarctions and have failed to show efficacy (De Keyser et al, 1999). This inclusion of subjects who are not primarily targeted by the drug could explain the failure of those trials.

Another potential tradeoff exists between the allowable treatment window and ease of recruitment (Elkins et al, 2006). This is because the shorter the time window after the stroke that is eligible for entry, the harder it will be to recruit. Yet recombinant tissue-type plasminogen activator (rt-PA), which is as of now the only USFDA-approved drug for acute ischemic stroke, has to be given within a short time after symptom onset in order to be most effective. In this case of treatment within 180

minutes of symptom onset, it will be more difficult to recruit patients.

Trials with large numbers of study centers have been less efficient in recruiting subjects, and competition among trials can be a limiting factor as well (Adams et al, 1995). Therefore, if multiple stroke trials are being conducted in the same center, it would be advisable that the inclusion criteria not overlap, unless enough patients are available to satisfy recruitment in all of the trials, in which case overlap would not matter. The development of regional acute stroke referral networks is a step in a positive direction, which should greatly support recruitment in stroke trials by directing patients to trials for which they would be eligible.

In the recruiting process itself, private practitioners should be aware of the principle of ''equipoise'' (Lader et al, 2004). This means that the physician expresses uncertainty toward which arm of a particular study is more effective (ie, not sure if treatment A is better, worse than, or equal to treatment B). Clinicians must set their personal beliefs and interests aside and rely on the fact that the trial is being conducted because no definitive, evidence-based data yet exist, (''if we knew what we were doing, it would not be research''). In the case where an effective, proven treatment (a standard of care) is already available, it would be unethical to include a placebo arm to the study. Exceptions to this rule include trials for minor conditions where temporary omission of treatment would cause no serious harm, and circumstances in which there are ''compelling scientifically sound methodologic reasons'' to use a placebo (Lader et al, 2004). A trial for acute cerebral infarct now is unlikely to have a placebo arm because rt-PA has been approved as the standard drug.

Many centers performing clinical trials, both academic and private practice, advertise their involvement in a given trial. This can be done through newspapers, magazines, radio, Internet/Web site, brochures, and community lectures. Some of the benefits of advertising include enhanced recruitment, promotion of new and promising treatments within the community, and support of local stroke center awareness and activities. Some of the cons of advertising include competitive feelings among others in the community not doing similar trials and the potential appearance of self-promotion.

A relatively new obstacle to enrollment into clinical trials is the issue of potentially biased sampling. As the number of simultaneously enrolling clinical trials has increased and the growing number of available but unproven therapies (off-label medication use or devices) has increased, the importance of considering biased enrollment and resulting slow enrollment in some cases has come to the forefront of clinical trial obstacles. Physicians who agree to participate in stroke trials must carefully consider this issue and agree to invite all eligible patients to participate in the trial. This may mean declining participation in other overlapping trials and/or not offering unproven therapies for patients who are eligible for the trial.

INFORMED CONSENT

Informed consent is the mandatory process of allowing the patient or surrogate consent provider to understand the procedures and treatments and the risks and benefits of the study. It must be explained that it is our (the investigator's) lack of knowledge of what constitutes best care that allows us to invite participation. Informed consent is the actual discussion process; the signed consent form, although necessary, is simply the documentation of that conversation.

The physician or staff enrolling the potential participant must explain in

KEY POINTS

- In the recruitment process itself, private practitioners should be aware of the principle of ''equipoise.''
- Informed consent is the mandatory process of allowing the patient or surrogate consent provider to understand the procedures and treatments and the risks and benefits of the study.

KEY POINTS

- It is important to remember that the case report forms for the study must be kept separate from the patient's clinical care record, both for data source verification and for confidentiality.
- Typically, study monitors conduct regularly scheduled site visits in order to perform data verification from source documents (eg, hospital records, office charts, laboratory reports, radiology reports) and ensure that the study data are an accurate and valid representation of the patient's medical status.

detail what the study will involve, making sure to maintain equipoise. Participation should be completely voluntary, and the physician must let patients know that a decision not to participate will not negatively affect their future care. It is important to keep in mind that patients' belief systems and values will heavily influence their views about whether or not to participate in a clinical trial. Study personnel must be knowledgeable about these aspects of a patient's individuality, respect them, and work within them to help the patient feel positive about trials in general and participating in a specific trial.

If possible, it is preferable for someone other than the treating physician to obtain informed consent to avoid potential conflict of interest and potential patient duress. This position is strongly encouraged by the American Medical Association.

DATA COLLECTION AND MANAGEMENT

Most clinicians in practice are most familiar and comfortable with free-style documentation in an office chart or hospital record (with possible subsequent dictation). However, documenting clinical, laboratory, and radiologic data on a patient enrolled in a clinical trial is typically performed on case report forms (CRFs), which are standardized and typically require more detailed information than that reported in an office visit or hospital consultation. For a given trial or registry, however, the forms could be as brief as one page or involve several detailed and longer forms. The key is capturing valid data.

It is important to remember that the case report forms for the study must be kept separate from the patient's clinical care record, both for data source verification and for confidentiality.

The standardization is necessary so that the same information is obtained on every patient in the trial. Without this information, potential confounding variables that could influence treatment responses, outcome, or safety of the medication could not be rigorously and properly assessed.

Data collection must be consistent throughout the trial, and certain standardized outcome measures should be used. These typically would include the NIH Stroke Scale (NIHSS). Standardization of outcome measures allows for various trials to be easily compared later on. As shown by migraine trials, meta-analyses and head-to-head comparisons remain powerful tools for looking at the results from several trials. However, head-to-head trials are the criterion standard for comparison between treatment approaches (Tfelt-Hansen, 2006).

During the trial, it is important to collect data in a timely manner. It is more difficult to try to reconstruct or determine missing data after long periods of time than after days to a week. Data will generally be reviewed by external study personnel and edited in order to maintain the quality of the results. Typically, study monitors will conduct regularly scheduled site visits in order to perform data verification from source documents (eg, hospital records, office charts, laboratory reports, radiology reports) and ensure that the study data are an accurate and valid representation of the patient's medical status. These visits usually occur on a regularly scheduled basis, either a certain number of times per year or after a certain number of patients are enrolled at that site.

Table 7-2 provides an example of a typical table of contents for the write-up of a study, which includes topics that need to be addressed.

SAFETY REPORTING

Safety reporting is an essential aspect of the conduct of a clinical trial, and

clinical trial personnel must understand and appreciate the issues involved, as well as the legal requirements. Any clinical, laboratory, or radiologic abnormality that occurs during the course of the clinical trial has to be judged, both by the local investigator and often by an independent medical monitor, as to the degree of relatedness of the event to the study protocol, drug, or device.

Standard definitions are used for reporting specific types of safety data, including adverse events (AE), adverse reactions (AR), serious adverse events (SAE), serious adverse reactions (SAR), and suspected unexpected serious adverse reactions (SUSAR); and each type has different reporting requirements. AEs and SAEs are any events that occur during time of trial but not necessarily related to treatment or trial. Further details of these respective terms are beyond the scope of this article but can be found at *www.admin.ox.ac.uk/rso/clinical/conduct.shtml*.

TABLE 7-2 Protocol Table of Contents

- Introduction
- Objectives
- Study design summary
- Study population
- Inclusion/exclusion criteria
- Study size justification
- Dosage and administration
- Efficacy, pharmacokinetics, and safety evaluations
- Data analysis methods
- Informed consent, ethical review, and regulatory considerations

Adapted with permission from Chappell AS. Pearls and pitfalls of clinical trial investigation: should I get involved in the drug development process? Semin Neurol 2001;21(4):417–424.

Above all, the key message is that safety comes first.

UNDERSTANDING OUTCOME MEASURES TO ENHANCE TRIAL CONDUCT

Practice-based research participation requires some understanding and appreciation for deciding how a treatment can actually be determined to be beneficial. In order to scientifically determine a therapeutic effect, there must be a measurable, quantitative difference in the primary outcome measure between the experimental therapy and the standard treatment (or placebo).

When thinking about what outcome measures to use, it is important to consider what factors are most relevant to the patient. For example, patients' ability to participate in various activities upon recovery will be more important to them than the amount of reduction of brain damage that has occurred. From a review including 51 acute stroke trials, only 29 specifically defined the primary end points used. Looking at all measures of outcome from those trials (**Table 7-3**), only one study reported a measure for quality of life, and none included a measure of participation (Duncan et al, 2000). Even though approximately 75% of the studies included a measure of activity, 11 different measurement tools were used. The modified Rankin Scale (mRS) and Barthel Index (BI) were the most commonly used scales for measuring activity, but having so many others makes comparisons across studies more complicated. In addition, even when the same scale was used, cutoff points between a favorable and an unfavorable outcome varied (Duncan et al, 2000).

Clinical trials grapple with optimizing the time that is best for determining an end point. As a result, there has been inconsistency in the timing of these assessments. Time of recovery does vary as a function of the severity

KEY POINTS

- Above all, the key message is that safety comes first.
- Practice-based research participation requires some understanding and appreciation for deciding how a treatment can actually be determined to be beneficial.
- Clinical trials grapple with optimizing the time that is best for determining an end point.

KEY POINT

- A trial can offer new hope to patients who cannot be treated satisfactorily with the drugs that are currently available.

TABLE 7-3 End Points (Clinical Outcomes) Measured

End Point/Clinical Outcomes	Studies, n	Used as Primary End Point, n
Pathophysiologic parameters (eg, blood pressure, coagulation, hematocrit, recanalization)	9	1
Death	34	12
Impairment	42	7
Activity[a]	39	20
Participation	0	0
Quality of life/health status	1	0
Combined or global score	4	1

[a]Rankin Scale categorized as activity.

Adapted with permission from Duncan PW, Jorgensen HS, Wade DT. Outcome measure in acute stroke trials: a systematic review and some recommendations to improve practice. Stroke 2000;31(6):1429–1438.

of the stroke, but there should still be a standard time to assess final outcome. On average, spontaneous recovery plateaus in patients taking a placebo have occurred 5 to 6 months after the stroke; yet the most commonly used time frame in the studies that were surveyed was only 3 months (**Figure 7-5**). To solve these issues, it is essential to define a standard set of outcome measures for acute stroke trials. Cutoff points should not be chosen arbitrarily, but the whole range of data should be taken into account using statistical analysis. Timing of assessments should be consistent, and certain measures, such as quality of life, should be given greater importance (Duncan et al, 2000).

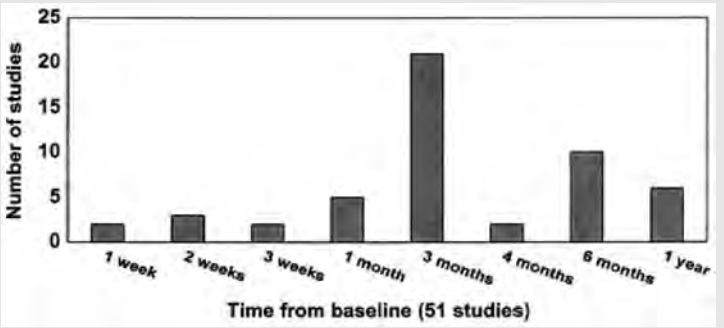

FIGURE 7-5 Time frame of final outcome assessment.

Reprinted with permission from Duncan PW, Jorgensen HS, Wade DT. Outcome measure in acute stroke trials: a systematic review and some recommendations to improve practice. Stroke 2000;31(6):1429–1438.

LESSONS FROM OTHER DISEASES

Epilepsy and migraine trials are a valuable source of wisdom for conducting clinical trials in the private practice setting. Epilepsy trials have shown that it is feasible to run clinical trials and at the same time continue to see patients regularly without much interference. The main advantage of enrolling patients directly from the private practice is quick entry into clinical trials, as well as a more user-friendly environment. The patients have the possibility of participating soon after they are first diagnosed, and their physician can guide them through the process. A trial can offer new hope to patients who cannot be treated satisfactorily with the

drugs that are currently available. As an example, one private practice center in Australia was able to successfully incorporate clinical trials of antiepileptic drugs into its program by working with a pharmaceutical industry representative as well as colleagues from teaching hospitals (Beran and Tilley, 1994). The local teaching hospital offered support in terms of training, which was done using an apprentice approach, where responsibility is transferred gradually. Before starting, it was confirmed that the center had the necessary facilities, equipment, and staff for conducting the trials. More staff had to be hired to reduce waiting times for the regular patients, and a practice manual had to be created for reference by the new staff when needed. Many patients felt comfortable participating in clinical trials in this setting, and some also appreciated the opportunity to interact in the waiting room with others who had the same problem. Thus, there was also a psychosocial factor to patient satisfaction. These aspects of an epilepsy trial could translate well to stroke prevention RCTs for patients with recent strokes seen in a similar practice setting.

Potential barriers to success also exist. Epilepsy trials have shown that certain obstacles can present when trying to translate the results of clinical trials to practice. Because the trials have a rigorous protocol and design, it is hard to generalize their results. The goal with a new drug is to use it so that all patients will benefit from maximum efficacy and experience a minimum of adverse effects. In the usual therapeutic setting, treatments must be individualized. This situation differs from that of a clinical trial, in which everything, ranging from dosage to timing, is standardized for control purposes. The ultimate goal for the patient is good overall health, not just stopping the seizures that result from epilepsy. Clinicians must remember this when getting involved with clinical trials and subsequently having to interpret results for use in their practice (Gilliam, 2005).

Some strategies can be learned from migraine trials. It is necessary to realize that there are many possible goals for the results of a clinical trial, and it is important to know which one in particular is being pursued. The usual main purpose of clinical trials is to determine a new drug's efficacy (compared with a placebo or a standard drug). This could mean that the new drug is more efficient, that it has fewer adverse effects, or a combination of the two. In migraine trials that involved various types of triptans, for example, pharmaceutical companies worked toward different goals depending on which triptan they chose to investigate. For instance, one company tried to achieve a better complete response; another tried to lessen adverse effects and recurrences; and yet another tried to achieve a quicker onset of action (Tfelt-Hansen, 2006). There are many ways to improve a current drug, and all of these are valid approaches.

A VIEW INTO THE FUTURE: TELEMEDICINE FOR STROKE

Telemedicine may also be a helpful tool to offer faster treatment to patients with acute stroke (Levine and Gorman, 1999; Schwab et al, 2007) by including rural hospitals that have not previously given acute thrombolytic therapy (Hess et al, 2006). Stroke specialists from the academic medical center can help diagnose patients in emergency situations and assess whether they could be candidates for a particular trial. This is especially useful for experimental treatments with a short allowed treatment interval, as the diagnosis through telemedicine would be much faster than

KEY POINTS

- Telemedicine allows for faster treatment in hospitals that have no stroke specialist, and this would increase the pool of patients available for time-sensitive clinical trials.
- The clinical practice setting typically reflects standard patient care more closely than academic medical centers and, therefore, could enhance patient recruitment and management.

having the specialist travel to the patient's bedside in a remote emergency department. This approach has the potential to allow for more patients to be involved in clinical trials, presently through transfer of the patient from the remote site to the academic medical center (hub). Currently we are unaware of any RCTs being conducted at remote/private practice sites using an experimental therapy. Two RCTs that are comparing telestroke to conventional care are in progress (ClinicalTrials.gov NCT00283868 at Bichat Hospital in France and ClinicalTrials.gov NCT00279149 at UCSD).

Telemedicine has been shown to allow for faster treatment in hospitals that have no stroke specialist, and this would increase the pool of patients available for time-sensitive clinical trials (Fisher, 2005; Levine and Gorman, 1999).

SUMMARY

Clinicians in private practice interested in participating in clinical research should have the following requirements: motivation, staff support (data collection requirements), and liability insurance for protection against claims arising out of damage from the new treatment. The practitioner should carefully read the Clinical Investigator's Brochure and protocol. The clinical practice setting typically reflects standard patient care more closely than academic medical centers and, therefore, could enhance patient recruitment and management.

Participation in clinical research is voluntary for patients. The availability of clinical trials increases their options and potentially improves their care. For doctors/researchers, participation allows them to make a long-lasting contribution to the health and well-being

TABLE 7-4 Useful Web Sites for Information on Participation in Clinical Trials

- Stroke Trials Registry. *www.strokecenter.org/trials.* Accessed October 30, 2007.
- US Department of Health and Human Services. National Institutes of Health (NIH). *www.nih.gov.* Accessed October 30, 2007.
- *nihroadmap.nih.gov*.
- National Institute of Neurological Disorders and Stroke. NINDS Clinical Research Collaboration. *nindscrc.org.* Accessed October 30, 2007.
- National Institute of Neurological Disorders and Stroke. NINDS Clinical Research Collaboration. *www.ninds.nih.gov/funding/research/clinical_research/crc.htm*. Updated October 10, 2007. Accessed October 30, 2007.
- US National Institutes of Health. ClinicalTrials.gov. *clinicaltrials.gov.* Accessed October 30, 2007.
- Sephmer Sciences. GCP/Ethics—preparing research investigators. *www.sephmersciences.com/Test.html*. Accessed October 30, 2007.
- US Food and Drug Administration. Clinical trials—information for health professionals. *www.fda.gov/oc/gcp/*. Accessed October 30, 2007.
- CenterWatch. Background information on clinical research. *www.centerwatch.com/patient/backgrnd.html*. Accessed October 30, 2007.
- University of Oxford. Research services: clinical trials—trial conduct. *www.admin.ox.ac.uk/rso/clinical/conduct.shtml*. Accessed October 30, 2007.

of their patients in conjunction with their colleagues from all over the country and/or world, which they would not be able to make alone. A list of Web sites to help the clinician make an educated decision about clinical trial participation is provided in **Table 7-4**. Clinical research is optional, but potentially beneficial, for physicians, patients, and populations who have the opportunity to participate.

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REFERENCES

Adams RJ, Fisher M, Furlan AJ, del Zoppo G. Acute stroke treatment trials in the United States. Rethinking strategies for success. Stroke 1995;26(12):2216–2218.

Beran RG, Tilley M. Clinical trials of antiepileptic drugs performed in the private practice setting. Epilepsia 1994;35(1):101–106.

Burgin WS, Staub L, Chan W, et al. Acute stroke care in non-urban emergency departments. Neurology 2001;57(11):2006–2012.

Chappell AS. Pearls and pitfalls of clinical trial investigation: should I get involved in the drug development process? Semin Neurol 2001;21(4):417–424.

Chen DT, Worrall BB. Practice-based clinical research and ethical decision making—Part I: deciding whether to incorporate practice-based research into your clinical practice. Semin Neurol 2006a;26(1):131–139.

Chen DT, Worrall BB. Practice-based clinical research and ethical decision making—Part II: deciding whether to host a particular research study in your practice. Semin Neurol 2006b;26(1):140–147.

De Keyser J, Sulter G, Luiten PG. Clinical trials with neuroprotective drugs in acute ischaemic stroke: are we doing the right thing? Trends Neurosci 1999;22(12): 535–540.

Duncan PW, Jorgensen HS, Wade DT. Outcome measure in acute stroke trials: a systematic review and some recommendations to improve practice. Stroke 2000;31(6):1429–1438.

Elkins JS, Khatabi T, Fung L, et al. Recruiting subjects for acute stroke trials: a meta-analysis. Stroke 2006;37(1):123–128.

Fisher M. Developing and implementing future stroke therapies: the potential of telemedicine. Ann Neurol 2005;58(5):666–671.

Gilliam FG. Epilepsy—success in clinical practice: translating trials to practice. Eur J Neurol 2005;12(suppl 4):22–29.

Hess DC, Wang S, Gross H, et al. Telestroke: extending stroke expertise into underserved areas. Lancet Neurol 2006;5(3):275–278.

Johnston SC, Rootenberg JD, Katrak S, et al. Effect of a US National Institutes of Health programme of clinical trials on public health and costs. Lancet 2006;367: 1319–1327.

Lader EW, Cannon CP, Ohman EM, et al. The clinician as investigator: participating in clinical trials in the practice setting. Circulation 2004;109(21):2672–2679.

Levine SR, Gorman M. "Telestroke": the application of telemedicine for stroke. Stroke 1999:30(2):464–469.

Lyden PD, Rapp K, Babcock T, Rothrock J. Ultra-rapid identification, triage, and enrollment of stroke patients into clinical trials. J of Stroke Cerebrovasc Dis 1994;2: 106–113.

Ross S, Grant A, Counsell C, et al. Barriers to participation in randomised controlled trials: a systematic review. J Clin Epidemiol 1999;52(12):1143–1156.

Schwab S, Vatankhah B, Kukla C, et al, Long-term outcome after thrombolysis in telemedical stroke care. Neurology 2007;69(9):898–903.

Tfelt-Hansen P. Understanding clinical trials in migraine. J Headache Pain 2006;7(2): 101–108.

ADDITIONAL REFERENCES AND SELECTED READING

Beran R, Beran ME. Conduct of trials in private clinical practice. Epilepsia 2000;4(7)1: 875–879.

Jain KK. Clinical trials in neurology: clinical summary. MEDLINK. *www.medlink.com*. Accessed August 8, 2008.

LaMonte MP, Bahouth MN, Hu P, et al. Telemedicine for acute stroke: triumphs and pitfalls. Stroke 2003;34(3):725–728.

Morin K, Rakatansky H, Riddick FA Jr, et al. Managing conflicts of interest in the conduct of clinical trials. JAMA 2002;287(1):78–84.

Pace WD, Staton EW, Holcomb S. Practice-based research network studies in the age of HIPAA. Ann Fam Med 2005;3(suppl 1):38–45.

APPENDIX
Stroke Coding Guide for Critical Care Coding

Critical Care *CPT*® codes can be used for managing an unstable, critically ill stroke patient. The progress or admitting note must mention the time spent that day and should state that the patient is ''unstable, critically ill.'' We recommend that the latter is an explicit statement in the Impression.

The critical care codes do not use bullet points. There are no other criteria for content of the notes, beyond specifying the total time spent and clarifying that the patient is unstable and critically ill.

A stroke patient is unstable and critically ill when there is a high probability of imminent life-threatening deterioration. Many stroke patients meet that criterion. Note that a therapy, such as IV tPA, qualifies for critical care coding when it creates a high risk of a life-threatening intracranial bleed.

The critical care codes are used by the physician(s) managing the patient. They are not used by consultants. More than one physician can use the codes each day if each manages an aspect of the patient's critical illness.

There are two codes: one for the first hour (99291), the other for each additional half-hour (99292). The second code can be used in multiple units.

More Than One Neurologist: Sometimes more than one neurologist manages the patient that day. For example, the covering physicians rotate at mid-day. One provides care for the first 12 hours, and the other for the second 12 hours.

If the physicians are from the same group and share the same Medicare provider number, then they should aggregate (add together) their time and bill once. The second shift physician should document in his or her note the total time spent by both physicians, and bill accordingly for the combined time.

More Than One Specialty: Sometimes a neurologist manages the stroke and another specialist manages a different part of the patient's care at the same time, such as ventilator management by an ICU physician. Both may use the critical care codes.

Location: These codes can be billed at any location, eg, emergency department (ED), radiology, floor bed, or ICU. The time spent must track where the patient is. As an example, a physician spends 45 minutes with the patient in the ED evaluating and arranging the admission, then 45 minutes with the patient in radiology completing the examination and reading the imaging as it appears, and another hour with the patient in the ICU organizing the admission management and testing. In that case, all 2 hours 30 minutes is billable critical care time.

Time in Other Locations: If the patient is already in the ICU, then time does not count toward the total when spent off the floor away from the patient at radiology reviewing images or at the office making phone calls. Time only counts when it is spent on the unit where the patient is.

Family Time: If the patient cannot speak for him/herself, then the family is expected to speak for the patient. Time then counts toward the total critical care time when it is spent explaining the situation to the family, obtaining additional history, and discussing treatment options. If the patient is able to speak for him/herself, then family time only counts if the patient is present.

Resident's Time: Time spent by residents, or medical students, does not count toward total critical care time. Only the time spent by a billing attending counts.

E/M Code and Critical Care Billing: Both can be billed if both services were provided. The record should document that the E/M service was separate from [that] of the critical care service. Both services must be documented. Particular time spent can be counted either for the E/M or for the critical care service, but not for both.

CPT® INSTRUCTIONS FOR USING THE CRITICAL CARE CODES—OFFICIAL DETAILS:

99291 Critical care, evaluation and management of the critically ill or critically injured patient; first 30 to 74 minutes

99292 Each additional 30 minutes (List separately in addition to code for primary service.)

Code 99291 is used to report the first 30 to 74 minutes of critical care on a given date. It should be used only once per date even if the time spent by the physician is not continuous on that date. (Note: All time from a given date should be noted in the patient record and totaled for the entire date to determine the appropriate amount of critical care time to bill for.)

Total Duration of Critical Care	Codes
Less than 30 Minutes	***Appropriate E/M Codes***
31 to 74 Minutes (1/2 Hour to 1 hour 14 minutes)	99291 × 1
75 to 104 Minutes (1 Hour 15 minutes to 1 hour 44 minutes)	99291 × 1 and 99292 × 1
105 to 134 Minutes (1 Hour 45 minutes to 2 hours 14 minutes)	99291 × 1 and 99292 × 2
135 to 164 Minutes (2 Hours 15 minutes to 2 hours 44 minutes)	99291 × 1 and 99292 × 3
165 to 194 Minutes (2 Hours 45 minutes to 3 hours 14 minutes)	99291 × 1 and 99292 × 4
194 Minutes or longer (3 Hours 15 minutes, etc)	99291 and 99292 as appropriate (see illustrated reporting examples above)

Critical care is the direct delivery by a physician(s) of medical care for a critically ill or critically injured patient. A critical illness or injury acutely impairs one or more vital organ systems such that there is a high probability of imminent or life-threatening deterioration in the patient's condition. Critical care involves high complexity decision making to assess, manipulate, and support vital system function(s) to treat single or multiple vital organ system failure and/or to prevent further life-threatening deterioration of the patient's condition.

Providing medical care to a critically ill, injured, or postoperative patient qualifies as a critical care service only if both the illness or injury and the treatment being provided meet the above requirements. Critical care is usually, but not always, given in the critical care area, such as the coronary care unit, intensive care unit, pediatric intensive care unit, respiratory care unit, or the emergency care facility.

Note: For the purposes of reporting critical time, the "unit" constitutes the location of the patient. For example, if the physician accompanies the patient to radiology to view scans this can be included in critical care time.

Critical care may be provided on multiple days, even if no changes are made in the treatment rendered to the patient, provided that the patient's condition continues to require the level of physician attention described above.

Critical care and other E/M services may be provided on the same patient on the same date by the same physician.

Note: When two physicians from the same group are billing for critical care, total time for each physician should be added together and billed under one physician's tax ID number; two physicians from different groups may also bill for critical care as long as they are involved in different aspects of the patient's care.

Documentation

Time spent with the individual patient should be recorded in the patient's record. The time that can be reported as critical care is the time spent engaged in work directly related to the individual patient's care whether that time was spent at the immediate bedside or elsewhere on the floor or unit.

Also, when the patient is unable or clinically incompetent to participate in discussions, time spent on the floor or unit with family members or surrogate decision makers obtaining a medical history, reviewing the patient's condition or prognosis, or discussing treatment or limitations(s) of treatment may be reported as critical care, provided that the conversation bears directly on the management of the patient. Time spent in activities that occur outside of the unit or off the floor (eg, telephone calls, whether taken at home, in the office, or elsewhere in the hospital) may not be reported as critical care since the physician is not immediately available to the patient. Time spent in activities that do not directly contribute to the treatment of the patient may not be reported as critical care, even if they are performed in the critical care unit (eg, participation in administrative meetings or telephone calls to discuss other patients). Time spent performing separately reportable procedures or services should not be included in the time reported as critical care time.

Note: As there are not specific instructions other than this as to what should be documented, it is important to note in the patient's record that the patient is "unstable and critically ill." It is important to keep in mind that increased usage of critical care codes may prompt an audit; physicians should make sure that they are documenting correctly to ensure a positive outcome.

ACUTE STROKE CASES

Case 1. You are called to the ED to see a 68-year-old man with onset of aphasia and right hemiplegia 2 hours ago. You arrive in the ED at 6:00 PM and find him globally aphasic with no movement of the right extremities. NIHSS score is 18. CT brain was done before your arrival and you read it as normal. Laboratory values including glucose, platelets, and INR are all normal. His wife is in the room and you find he has a history of hypertension and atrial fibrillation. His medications include warfarin and Altace. He had no prior history of stroke and no recent trauma or surgical procedures. You ask the nurse for a blood pressure, which is 150/90 mm Hg. You complete the tPA checklist and decide he is an appropriate candidate for IV tPA. You explain the risks and benefits of IV tPA to his wife. She consents to proceeding with treatment. You ask the nurse to mix IV tPA and give him 0.9 mg/kg with 10% as a bolus. She mixes the tPA, draws the bolus into a syringe. You administer the bolus and the nurse starts the IV infusion of tPA. You write admission orders, dictate a note, and leave the ED at 7:10 PM.

Your note documents that you personally attended to this critically ill patient for 1 hour 20 minutes including acute stroke evaluation, determining the appropriateness of administering IV tPA, discussing with the family, and initiating treatment. This was exclusive of any time spent on E/M services.

Critical care time: 1 hour 20 minutes (80 minutes)

Billing codes: 99291, 99292

Case 2. You are called to evaluate a 58-year-old woman with aphasia and right hemiplegia. She was last observed to be neurologically normal at 8:00 AM. You arrive in the ED at 11:30 AM. You examine her and find an NIHSS score of 20. She has a normal blood pressure, normal laboratory values, and you read her CT as showing early hypodensity in the basal ganglia but otherwise no abnormality. You meet with her son and husband and explain that she is past the window for IV tPA but intraarterial thrombolysis or removal of the clot with the Merci® clot retriever are considerations. You explain the risks, benefits, and USFDA status of these treatments. They would like to proceed with angiography and possible clot lysis/removal. You call the interventional neurologist, and he asks that the patient be sent immediately to the angiography suite. You call anesthesia for intubation. The patient is sedated and intubated and you then accompany the patient to the angiography suite. The angiogram is started at 1:00 PM.

Angiography demonstrates complete occlusion of the left MCA. After discussion between you and the interventionalist, it is decided to attempt clot retrieval with the Merci device.

You leave at 1:30 PM. briefly to see another consult in the hospital. The interventionalist passes the clot retriever, but despite several attempts the MCA does not recanalize. You return to the angio suite at 2:00 PM. After discussion, you and the interventionalist decide to terminate the procedure, and the patient is transferred to the ICU at 2:30 PM. You write admitting orders for the ICU and dictate an admitting note documenting your history, examination, and your discussion with the family regarding risks and benefits. You also document that you were present during the interventional procedure except for 30 minutes, monitored the status of the patient, and contributed to the process of deciding on treatment. Total critical care time is 2 hours 30 minutes.

Critical care time: 2 hours, 30 minutes (150 minutes)

Billing codes: 99291, 99292 × 3

Case 3. You are called by a nurse in the ICU because a 31-year-old patient you had previously seen in consult with a large right hemisphere stroke is worse. You arrive in the ICU at 5:00 PM. Examination shows that he responds to voice by opening his eyes briefly but does not follow commands. The right pupil is larger than the left, irregular, and poorly responsive to light. He withdraws the right extremities to pain, but pinch on the left elicits extension of the left arm and triple flexion of the left leg. Both plantar responses are extensor. You determine that the mental status changes, papillary abnormality, and extensor plantar response on the right are new and suggest impending tentorial herniation. You call the neurosurgeon and order a stat CT scan. You order mannitol. As the nurses prepare the patient for transport to CT, you call the patient's wife and discuss the situation as well as the risks and benefits of decompressive craniotomy. His wife consents to the procedure. You accompany the patient to CT and immediately view the CT with the neurosurgeon who has now arrived. After discussion, the decision is made to proceed with decompressive craniotomy. The patient is taken emergently to the OR for the procedure at 6:50 PM.

You document the change in neurologic status, your discussion with the family and with the neurosurgeon. You state that you remained at the bedside of this critically ill patient through CT and the decision making process for a total of 2 hours.

Critical care time: 1 hour, 50 minutes (110 minutes)

Billing codes: 99291, 99292 × 2

The *Current Procedural Terminology, CPT*®, information is from *CPT*® 2007, Professional Edition, © 2006 American Medical Association. The text following the table is from page 19, ''Critical Care Services.''

Available at *www.aan.com/globals/axon/assets/2858.pdf.*

ETHICAL PERSPECTIVES IN NEUROLOGY

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The practice of neurology presents a series of ethical challenges for the clinician. These rarely have simple or straightforward solutions, but require careful consideration by the neurologist. This section of CONTINUUM, written by colleagues with particular interest in the area of bioethics, provides a case vignette that raises one or more ethical questions related to the subject area of this issue. The discussion that follows should help the reader understand and resolve the ethical dilemma.

LOCKED-IN SYNDROME: ENDOVASCULAR STROKE THERAPY AND END-OF-LIFE DECISIONS

NOTE: The following is based on an actual case.

A 33-year-old man presented to an emergency department with shortness of breath and altered mental status. He was awake and following commands on arrival, but was nonverbal. His mental status declined, and he became unresponsive. An MRI of the brain showed acute bilateral pontine infarctions consistent with basilar artery thrombosis. He was transferred to a hospital with a neuro-intensive care unit (ICU) and neuroendovascular interventional capabilities. There, he was intubated. His examination was consistent with locked-in-syndrome (LIS) with quadriplegia, ophthalmoplegia, and anarthria. Immediately upon admission he had the ability to communicate using eye blinking. Attempts to treat the midbasilar artery occlusion with balloon angioplasty resulted in partial recanalization but no clinical improvement.

The family members were uncertain of the patient's wishes and whether he would like to be sustained on artificial life-support measures. He did not have a living will, and initially it was difficult to determine whether he was conscious. The family was ambivalent about the plan of care, and was unable to come to a decision. As a result, full support was maintained. The patient gradually became more alert and was able to communicate with eye blinking, but the family and some members of the ICU team were uncertain about his comprehension and ability to make decisions. This case generated much discussion among the health care team about futility of care, quality of life, power of attorney, and burden to the community.

COMMENT

▶ The term *locked-in* was first described by Plum and Posner in 1966 to describe the clinical condition of quadriplegia, lower cranial nerve palsies, and anarthria with preserved consciousness. It is difficult to ascertain whether patients with LIS can understand or communicate complex concepts, which makes the assessment of

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decision-making capacity in LIS very difficult. If a patient is incorrectly determined to *have* decision-making capacity when it is actually lacking, then the eye-blinking pattern may wrongly be interpreted as informed communication. On the other hand, if a patient is incorrectly determined to *lack* decision-making capacity when it is actually present, then the patient's surrogate may make decisions that are either consistent or inconsistent with the patient's actual wishes. It is possible that the patient could be fully aware of the decisions, which would potentially add further emotional and psychological stress if the decision made is counter to the awake patient's wishes.

DISCUSSION

▶ It is well known that patients with LIS can retain their cognitive abilities and recover enough function to be able to communicate. For example, the 1997 book *The Diving Bell and the Butterfly* is the memoir of Jean-Dominique Bauby, who developed LIS as a result of a stroke at age 43. Bauby "dictated" the memoir to an assistant by eye blinks and a communication board. In describing living in the LIS state, he eloquently recounts the onset of his stroke, "Half conscious, I feel extremely strange, as if I had swallowed an LSD tablet…Not for a second does it occur to me that I may be dying…Then I sink to coma" (Bauby, 1997).

Not all patients with LIS, however, regain full consciousness, and the rate of recovery of consciousness is hard to predict. Especially if the patient neither has an advance directive nor has discussed such a scenario with family or friends, this leaves the patient's family and the ICU team with the dilemma of deciding how long to continue ICU treatment while waiting for communication capacity to return. Furthermore, even if the ability to communicate is established, it is especially challenging to determine comprehension and decision-making capacity when the ability to communicate is limited to eye blinking or eye movements.

There is evidence to suggest that the recovery of communication capacity takes months, which may mean that decisions to withdraw life-sustaining therapies should be delayed, especially if the goal is to allow the patient the opportunity to participate in the decision. Family members are the first to notice that the patient is able to communicate in over 50% of cases, with a mean time to recognition of the LIS (ie, recognition of consciousness) of 78 days (Leon-Carrion et al, 2002). Such a long wait, however, is likely to extend beyond the initial ICU admission, and arrangements would need to be made to reevaluate the patient's ability to communicate at regular intervals. Ideally this should be done by neurologists or rehabilitation specialists familiar with LIS and also should incorporate efforts by communication experts, possibly with facilitated communication devices and methods. Actual physician practices, however, may vary. A 1997 survey of 93 physicians treating patients with LIS found that 55% recommended intubating the patient in the presence of swallowing disturbances and imminent aspiration, 38% were in favor of stopping intensive care, 52% advocated not treating severe infections with antibiotics, 58% were in favor of discussing these problems in detail with the patient, and 87% advocated discussing them with relatives (Thiel et al, 1997).

Surrogate decision making is well known to be fraught with uncertainty. In the case of LIS, health care professionals and even family may assume that the quality of life of a patient with LIS is so poor and limited that it is not worth living. Thus,

knowledge of long-term outcomes is important. The 5-year and 10-year survival rates may be as high as 85% (Casanova et al, 2003; Doble et al, 2003). Interviews with the families and caretakers of long-term survivors of LIS suggest that these patients can develop meaningful roles in their families and communities, despite their severe impairment (Doble et al, 2003). The 1993 AAN position statement on the care of irreversibly paralyzed patients with retained consciousness and cognition recommends regularly reassessing patients' general medical condition, psychological state, and cognitive and communicative abilities to assure their ability to make sound decisions about sustaining or withholding life-support measures (American Academy of Neurology, 1993).

Not all physicians and nurses in the ICU setting may be willing to sustain a patient with possible LIS whose outcome requires prolonged ICU support, as they may consider such care futile. Health care professionals sometimes use their own views and biases of long-term outcome when advising families about early decisions, which is why familiarity with outcomes research is important. Nonetheless, there may still be health care professionals who feel they cannot participate in the care of such patients or who feel that such care is burdensome to society. Consultation from a hospital ethics committee can be helpful, as can consultation from a specialist familiar with outcomes in LIS. If a patient with LIS is determined to have both the capacity to communicate and make informed decisions, and if the patient wishes to have treatment continued, then there is little ethical foundation for health care professionals to refuse to participate in the patient's care. On the other hand, if the patient lacks capacity, or if surrogate decision makers have asked for care that the health care professionals believe is causing more burden than benefit to the patient, an option is to request not to be assigned to the patient's care, but in doing so, it is important that neither the patient nor the family be abandoned.

Family members carry a great burden and responsibilities when a patient has no advance directive and has not had prior discussions about goals of care. Furthermore, few patients would ever have contemplated an illness that would leave them quadriplegic, mute, wheelchair bound, and ventilator dependent. It is not surprising that conflicts can arise within the family over decisions to be made.

First and foremost for the ICU team caring for the patient and family is to acknowledge their burden and the uncertainty of the circumstances and to offer to help them make the best decisions they can. Considering the length of time necessary for patients with possible LIS to recover to the point that their ability to communicate is established, requests from the family for more time to observe the patient's response to therapy are probably reasonable. The ICU team can use this time to provide the family with an overview of the LIS and its long-term outcomes. As for establishing the emergence of the patient's communication ability, the family can be encouraged to establish an eye-blinking communication code with the patient. Once the communication code is established, it can then be determined whether the patient has decision-making capacity and (even more important) whether the patient wishes to make decisions. All autonomous patients have the option of deferring decision-making authority to someone else, and this option should be discussed and offered to patients with LIS who may find such complex communication so difficult that they would rather their surrogate make such decisions for them. Even if this is the case, it is important for the surrogate and the ICU team to inform the patient of the decisions they have made.

CONCLUSION

▶ In this case, after the patient became more alert and very brisk and consistent with his eye-blinking responses to the family's questions, the family gained confidence in his cognitive abilities and felt very strongly that he should make his own decisions. The patient wanted to be maintained on life-support measures. He is now thinking of writing his own memoir with encouragement from his family.

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REFERENCES AND SELECTED READINGS

Adams HP Jr, Adams RJ, Brott T, et al. Stroke Council of the American Stroke Association. Guidelines for the early management of patients with ischemic stroke: A scientific statement from the Stroke Council of the American Stroke Association. Stroke 2003;34(4):1056–1083.

American Academy of Neurology. Report of the Ethics and Humanities Subcommittee of the American Academy of Neurology. Position statement: Certain aspects of the care and management of profoundly and irreversibly paralyzed patients with retained consciousness and cognition. Neurology 1993;43(1):222–223.

Anderson C, Dillon C, Burns R. Life-sustaining treatment and locked-in syndrome. Lancet 1993;342(8875):867–868.

American Academy of Neurology. Position of the American Academy of Neurology on certain aspects of the care and management of profoundly and irreversibly paralyzed patients with retained consciousness and cognition. Report of the Ethics and Humanities Subcommittee of the American Academy of Neurology. Neurology 1993;43(1):222–223.

Bauby JD. The Diving Bell and the Butterfly. New York: Vintage International, 1997.

Casanova E, Lazzari RE, Latta S, Mazzucchi A. Locked-in syndrome: improvement in the prognosis after an early intensive multi-disciplinary rehabilitation. Arch Phys Med Rehabil 2003;84(6):862–867.

Doble JE, Haig AJ, Anderson C, Katz R. Impairment, activity, participation, life satisfaction and survival in persons with locked-in syndrome for over a decade. J Head Trauma Rehabil 2003;18(5):435–444.

Dumas A. The Count of Monte Cristo, London: Wordsworth Editions, 1997.

Leon-Carrion J, van Eeckhout P, Dominguez-Morales Mdel R, Perez-Santamaria FJ. The locked-in syndrome: a syndrome looking for a therapy. Brain Inj 2002;16(7):571–582.

Plum F, Posner JB. The diagnosis of stupor and coma. Philadelphia: FA Davis, 1966.

Thiel A, Schmidt H, Prange H, Nau R. Treatment of patients with thromboses of the basilar artery and locked-in syndrome: an ethical dilemma. Nervenarzt 1997;68(8):653–658.

Wijdicks EF, Scott JP. Outcome in patients with acute basilar artery occlusion requiring mechanical ventilation. Stroke 1996;27(8):1301–1303.

Zaidat OO, Tolbert M, Smith TP, Alexander MJ. Primary endovascular therapy with clot retrieval and balloon angioplasty for acute basilar artery occlusion. Pediatr Neurosurg 2005;41(6):323–327.

PRACTICE ISSUES IN NEUROLOGY

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In addition to the lifelong learning of new clinical and scientific knowledge, neurologists must understand the constantly evolving environment in which they practice. Changes occur rapidly in reimbursement and regulatory areas, in the integration of evidence-based medicine, and in the implementation of patient safety measures into clinical practice.

This section of CONTINUUM presents a case-based example of these issues as they relate to the clinical topic. These vignettes are written by neurologists with particular experience in systems-based practice and practice-based learning and improvement.

CASE

A 68-year-old man is evaluated in the emergency department because of aphasia and right-sided weakness. He was at a restaurant with his wife when he suddenly stopped speaking and fell to the floor unable to move his right side. Emergency medical services were called, and he was transported immediately to the emergency department. He arrived 1 hour after the onset of the deficit. A stroke code was called.

On examination, his NIH Stroke Scale (NIHSS) score is 20. He is mute and does not follow verbal commands. He has a left gaze deviation and does not respond to threat from the right. There are no movements of the right extremities. He has dense right facial weakness. He does not respond to pain on the right.

He has a history of atrial fibrillation treated only with aspirin. There is no prior history of stroke or TIA. His wife is present at the bedside and provides the history. CT of the brain is performed and shows no hemorrhage or early ischemic changes. Blood pressure is 150/85 mm Hg. International normalized ratio, platelet count, and blood glucose are all normal. The patient is considered a candidate for IV tissue plasminogen activator (t-PA). Because the patient is not competent to give informed consent, the patient's wife is advised of the risks and benefits of IV t-PA, including a 6% risk of intracerebral hemorrhage possibly causing neurologic worsening or even death. She is told that, despite this risk, more patients who receive t-PA recover from their strokes than those who do not. The patient's wife consents to proceeding with IV t-PA treatment, which is administered 1 hour and 40 minutes after stroke onset.

DISCUSSION

- In "Consent issues in the management of cerebrovascular diseases," a position paper of the AAN's Ethics, Law, and Humanities Subcommittee (1999), three elements were considered necessary and sufficient for a valid consent: adequate decision-making

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capacity, presentation of adequate information for an informed consent, and freedom from coercion. Adequate decision-making capacity requires that the patient is capable of understanding the relevant issues and can accurately convey his or her responses to the examiner. Many stroke patients would fall outside of this standard, particularly in the setting of impaired consciousness, aphasia, or significant cognitive deficits. Determining the necessary information regarding IV t-PA for the consent process is a significant challenge. The AAN guidelines specify that information must be adequate for a reasonable patient to make an informed decision, including risks and benefits, choice of options, and an explanation of a recommended course of action. In the case of IV t-PA, this information should include the increased short-term risk of hemorrhage and the potential long-term benefit of improved stroke outcomes. The decision-making process must not be unduly influenced by physicians, other family members, or any outside agency.

Discussion of the risks and benefits of IV t-PA may include a summary of the published studies. The National Institute of Neurological Disorders and Stroke (NINDS) t-PA trial randomized 624 patients treated within 3 hours of onset of stroke to treatment with either IV t-PA or placebo (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995). This study found an 11% absolute increase (55% relative) in favorable outcomes (NIHSS less than 1) at 90 days despite a 10-fold increase in intracerebral hemorrhage (6% versus 0.6%). There was no significant difference in mortality (17% versus 21%). The study has been criticized because of a baseline imbalance in stroke severity between the two groups. A subsequent reanalysis showed that even after statistical adjustment for this imbalance, patients were twice as likely to achieve a favorable outcome if they received IV t-PA (Ingall et al, 2004). Similar experience with IV t-PA has been reported for treatment of patients in community and academic hospitals outside the setting of randomized controlled trials (Albers et al, 2000; Tanne et al, 1999). Other trials of IV thrombolysis for acute stroke failed to find significant benefit, but longer time windows for initiation of treatment (6 hours) (Clark et al, 1999; Hacke et al, 1995; Hacke et al, 1998), the use of different thrombolytics (streptokinase) (Donnan et al, 1996; Multicenter Acute Stroke Trial—Europe Study Group, 1996; Multicentre Acute Stroke Trial—Italy [MAST-I] Group, 1995), and other methodologic differences make direct comparisons difficult. A pooled analysis of all prior IV t-PA trials confirmed the benefit of IV t-PA up to 3 hours after stroke onset and indicated the benefit extended to 4.5 hours (Hacke et al, 2004). The Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) registry of 6483 patients treated within 3 hours of stroke onset at 285 centers also found outcomes similar to those achieved in previous randomized controlled trials with no increase in hemorrhage rate or mortality (Wahlgren et al, 2007).

No general agreement exists on the extent of details necessary to properly advise a patient or surrogate regarding the risk and benefits of IV t-PA. The information included in the informed consent process varies and largely depends on the physician's level of comfort that sufficient information has been provided to allow an informed decision.

▶ Documentation of Informed Consent for IV t-PA

Some physicians and hospitals prefer a formal written consent documenting information regarding the risks and benefits signed by the patient or surrogate. Current American Heart Association/American Stroke Association guidelines do not support the need for a formal written consent (Adams et al, 2003), but recommend a detailed

discussion with the patients and their families providing potential risks and benefits associated with thrombolytic therapy. The discussion should be documented in the medical record, including the person or persons receiving the information, the content of the discussion, and the source of the consent. If consent is not given, the reasons for denial should be noted. When a surrogate is used for consent, the nature of the deficits that render the patient incapable of giving consent should be noted.

▶ Emergency Consent

In some cases, a patient is considered incapable of giving consent, and no surrogates are available in the emergent timeframe necessary for treatment with IV t-PA. In such situations, an exemption to the informed consent process exists that justifies initiation of treatment without specific consent (Fleck and Hayes, 2002). Four conditions should be met to invoke this exemption: (1) delay in treatment would have significant adverse effects; (2) no alternatives are available that would be equally effective but allow additional time for the consent process; (3) a reasonable person, if given sufficient time to consider the evidence, would agree to the treatment; and (4) the treatment should be considered as usual care. Most would agree that the first two conditions are satisfied for IV t-PA. Differences of opinion may exist regarding the third and fourth conditions, and physicians must decide for themselves whether the evidence regarding IV t-PA and the approval of the US Food and Drug Administration satisfies these criteria.

REFERENCES

Adams HP Jr, Adams RJ, Brott T, et al. Guidelines for the early management of patients with ischemic stroke: a scientific statement from the Stroke Council of the American Stroke Association. Stroke 2003;34(4):1056–1083.

Albers GW, Bates VE, Clark WM, et al. Intravenous tissue-type plasminogen activator for treatment of acute stroke: the Standard Treatment with Alteplase to Reverse Stroke (STARS) Study. JAMA 2000;283:1145–1150.

Clark WM, Wissman S, Albers GW, et al. Recombinant tissue-type plasminogen activator (alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS study: a randomized controlled trial. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. JAMA 1999;282(21):2019–2026.

Donnan GA, Davis SM, Chambers BR, et al. Streptokinase for acute ischemic stroke with relationship to time of administration: Australian streptokinase (ASK) trial study group. JAMA 1996;276(12):961–966.

Ethics and Humanities Subcommittee. Consent issues in the management of cerebrovascular diseases: a position paper of the American Academy of Neurology Ethics and Humanities Subcommittee. Neurology 1999;53(1):9–11.

Fleck LM, Hayes OW. Ethics and consent to treat issues in acute stroke therapy. Emerg Med Clin North Am 2002;20(3):703–715, vii–viii.

Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet 2004;363(9411):768–774.

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(13):1017–1025.

Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Lancet 1998;352(9136):1245–1251.

Ingall TJ, O'Fallon WM, Asplund K, et al. Findings from the reanalysis of the NINDS tissue plasminogen activator for acute ischemic stroke treatment trial. Stroke 2004;35(10):2418–2424.

Multicenter Acute Stroke Trial—Europe Study Group. Thrombolytic therapy with streptokinase in acute ischemic stroke. N Engl J Med 1996;335(3):145–150.

Multicentre Acute Stroke Trial—Italy (MAST-I) Group. Randomised controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischaemic stroke. Lancet 1995;346(8989):1509–1514.

The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333(24):1581–1587.

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(2):424–427.

Wahlgren N, Ahmed N, Davalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet 2007;369(9558):275–282.

CONTINUUM
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MULTIPLE-CHOICE QUESTIONS

These items are an integral part of the issue. They are not intended as an examination but rather as a means of stimulating thought and helping you assess your general understanding of the material presented in this issue. Some are designed to stimulate independent study; the comments and references provided with the preferred responses should assist in this process.

For each item, select the *single best response*, marking it on the answer form provided inside the back cover of this issue and return your completed form to the AAN. No formal grade is assigned, as the goal is to encourage critical thinking and self-assessment. Your responses will be kept completely confidential. By returning the completed answer form to the AAN, you earn up to 10 AMA PRA Category 1 Credits™. A transcript of credits earned in CONTINUUM will be sent to you within 2 months of receipt of your answer form.

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TYPE A QUESTIONS (ONE BEST ANSWER)

▶ **1.** An intraaortic balloon device that produces partial obstruction to aortic blood flow has been tested in small pilot studies as a therapy to improve stroke outcome. What is the guiding principle behind the use of such a device after stroke?

A. It disrupts cerebral autoregulation
B. It increases blood flow to the brain
C. It prevents further cerebral emboli
D. It prevents platelet aggregation
E. It raises systemic blood pressure

▶ **2.** A 70-year-old woman with a history of hypertension and type 2 diabetes is admitted to the hospital 1 hour after the acute onset of inability to move the left side. On admission, she has a left hemiparesis, greater in the arm than leg, and hemispatial neglect. MRI with diffusion-weighted imaging demonstrates an acute right middle cerebral artery infarct, and recombinant tissue-type plasminogen activator (rt-PA) is administered without complication. The stroke team is concerned about her inability to move the left leg well. If the follow-up head CT shows no intracranial hemorrhage, how long after

administration of rt-PA should the team wait before initiating deep venous thrombosis prophylaxis with anticoagulants?

A. 24 Hours
B. 3 to 4 Days
C. 7 to 10 Days
D. Contraindicated
E. Not contraindicated, but not useful

▶ **3.** A 47-year-old man is evaluated for acute onset of right hemiplegia. The MRI of the head shows an area of diffusion-weighted imaging/perfusion-weighted imaging mismatch on MRI. Which of the following mechanisms primarily leads to cell death in the jeopardized area of penumbra in this case?

A. Caspase-triggered nuclear fragmentation
B. Closure of mitochondrial permeability transition pore
C. Decreased expression of endothelial cell adhesion molecules
D. Phospholipase-induced membrane destruction
E. Total depletion of mitochondrial-produced adenosine-5′-triphosphate

▶ **4.** 70-year-old man with a history of hypertension and hyperlipidemia is transported within 30 minutes of the onset of acute inability to move his left side from a rural area to a hospital that is a designated primary stroke center. He is assessed by emergency medical services personnel in the field and by an emergency department physician on arrival. According to the authors of the chapter "Primary Stroke Center Certification," which of the following aspects of primary stroke center care may lead to a better outcome for this patient?

A. Any place that treats more strokes will be better at it
B. Experimental protocols can be used for difficult cases
C. The patient is more likely to receive recombinant tissue-type plasminogen activator
D. Physician reimbursement is better, so specialists are more likely to come in
E. Treatment is more conservative and less likely to produce morbidity

▶ **5.** A 55-year-old man is seen by the acute stroke intervention team 2 hours after acute onset of right-sided weakness and aphasia. Should this patient be eligible for treatment with tissue plasminogen activator (t-PA), which of the following tests should be conducted prior to initiating t-PA?

A. Arterial blood gases
B. Blood glucose
C. Chest x-ray
D. Liver function
E. Stool guaiac

▶ **6.** A 62-year-old woman is brought to the emergency department within 30 minutes of acute-onset left-sided weakness. Evaluation within 15 minutes of arrival reveals dense left hemiparesis and left gaze preference. Blood pressure is 200/115 mm Hg. A CT shows effacement of the gray-white matter junction in the right insula. EKG, cardiac enzymes, oxygen saturation, blood glucose, electrolytes and platelet count, prothrombin time, and activated partial thromboplastin time test results are normal. The patient has

no history of previous head trauma or stroke; cerebral, gastrointestinal, or urinary hemorrhage; recent arterial puncture; or seizures. Which of the following drugs is recommended for treatment of hypertension before considering administration of IV recombinant tissue-type plasminogen activator (rt-PCA) in this patient?

A. Clonidine
B. Enalapril
C. Hydralazine
D. Labetalol
E. Nifedipine

▶ **7.** In addition to the fact that timing of final assessments in stroke trials is not standardized, the authors of the chapter "'How To' Guide for Clinicians Interested in Becoming Involved in Clinical Stroke Research" state that there is little agreement on the best outcome measures to be used in acute stroke trials. Which of the following outcome measures is felt to be the most meaningful according to the authors?

A. Impairment measures
B. Measures of activity
C. Percent of brain tissue damaged
D. Prevention of future strokes
E. Quality-of-life questionnaires

▶ **8.** A group of neurologists servicing a large community hospital approach the board of directors and express their desire to organize a dedicated stroke unit. They provide information to the board that shows that functional outcomes in stroke units are superior and that benefits to patients are lasting. Which of the following is the most likely explanation for the improved outcomes in certified stroke units?

A. Availability of interventional radiology
B. Better nursing to patient ratio
C. Better prevention and treatment of infections
D. Higher profits increase future unit funding
E. Inclusion of rehabilitation services

▶ **9.** The use of several imaging techniques for rapidly and accurately identifying the ischemic penumbra in patients with stroke is discussed by the authors of the chapter "Emerging Therapies." Which of the following suggests a large area of penumbra?

A. Distal middle cerebral artery occlusion
B. Early ischemic changes on CT
C. Lacunar infarction in the internal capsule
D. Large diffusion-weighted imaging abnormality
E. Large diffusion-weighted imaging/perfusion-weighted imaging mismatch

▶ **10.** A 75-year-old man with a history of atrial fibrillation treated with warfarin presents to an urgent care clinic because of inability to use his left hand since awakening that day. He reports no pain or numbness in the hand but has been unable to raise his wrist. He states that he slept in his

bed last night, although he has a tendency to doze off in his recliner. He is also treated with atenolol for mild hypertension. On examination, cognition is normal. Blood pressure is 130/80 mm Hg, and heart rate is irregular at 60 beats per minute. He is unable to extend the left wrist or fingers. Forearm extensors are normal. There is no sensory deficit along the dorsal thumb. He is sent home from the urgent care center and referred to a neurologist. The neurologist suspects a central lesion. Presence of which of the following signs or symptoms may alert the clinician to the possibility of stroke as a cause of distal arm weakness?

A. Gradual onset
B. Headache
C. Sensory symptoms
D. Stroke risk factors
E. Unilateral involvement

▶ **11**. A 75-year-old man is brought by ambulance to an emergency department (ED) 30 minutes after the acute onset of right-sided weakness and difficulty speaking. He is seen by an ED physician, and a noncontrast CT scan of the brain is normal. He is felt to be a candidate for recombinant tissue-type plasminogen activator (rt-PA) and receives a bolus of the drug. He is then accepted for transfer to a major university hospital. What is the current policy on reimbursement for rt-PA infusion as it relates to this patient?

A. The facility with the greatest number of hospital days for poststroke care can bill
B. The first hospital cannot bill for rt-PA because it provided only a bolus
C. The first hospital cannot bill for rt-PA because it was not given by a neurologist
D. The first hospital cannot bill if it is not a certified stroke center
E. The second hospital cannot bill for rt-PA because it was initiated in another facility

▶ **12.** A 56-year-old right-handed man is evaluated for acute onset of right hemiplegia and aphasia. A CT scan of the head shows loss of gray-white matter differentiation in the left insular cortex and basal ganglia and a hyperdense left middle cerebral artery sign. There is an area of diffusion-weighted imaging (DWI)/perfusion-weighted imaging mismatch on MRI, suggesting an area of penumbra in the left cerebral cortex. Which of the following mechanisms accounts for increased DWI signal in this patient?

A. Acute inflammation
B. Increased blood-brain barrier permeability
C. Intracellular edema
D. Luxury perfusion
E. Myelin breakdown

▶ **13.** A 65-year-old man with new-onset atrial fibrillation is admitted to the hospital after awakening with right-sided weakness and difficulty producing the right word. He is diagnosed with an acute left middle cerebral artery

infarct and placed in a step-down unit. Initial nursing assessment notes that he coughs when attempting to swallow water. Which of the following measures is most likely to be effective in preventing the development of pneumonia in this patient?

A. Daily pulmonary function tests
B. Formal swallowing evaluation
C. Prophylactic antibiotics
D. Transfer to an intensive care unit
E. Urgent percutaneous endoscopic gastrostomy placement

▶ **14.** Among the advantages of intraarterial delivery of fibrinolytic agents is the ability to deliver high concentrations of drug directly to the clot with less systemic exposure to the agent. However, widespread use of this technique is most likely to be limited because of which of the following factors?

A. High incidence of distal emboli
B. Lack of general availability of fibrinolytics
C. Lack of trained radiology personnel
D. Prohibitive liability costs
E. Specialized facilities and expertise required for neurointerventional treatment

▶ **15.** A 72-year-old man with a history of hypercholesterolemia, hypertension, and an ST-elevation myocardial infarction 1 month ago is brought to the emergency department 60 minutes after acute-onset right-sided weakness and speech difficulties. Current medications include enalapril, atorvastatin, and aspirin. Evaluation reveals a right hemiparesis and global aphasia. Blood pressure is 170/100 mm Hg. A CT shows a hyperdense left middle cerebral artery and effacement of the gray-white matter boundary in the left insula. Cardiac enzymes, blood glucose, electrolytes, platelet counts, prothrombin time, and activated partial thromboplastin time are normal. Which of the following findings makes this patient ineligible for treatment with IV recombinant tissue-type plasminogen activator (rt-PA) according to current guidelines?

A. Aspirin use
B. Head CT scan findings
C. Hypertension
D. Recent myocardial infarction
E. Severity of neurologic deficit

▶ **16.** At the beginning of 2008, the Joint Commission established 10 stroke-specific care performance measures as required for primary stroke care center certification. Which of the following is included in that group of measures?

A. Anticoagulation for atrial fibrillation
B. Diabetes screening
C. Echocardiogram by day 2
D. Heparin for carotid artery disease
E. Repeat neuroimaging by day 2

▶ **17.** A neurologist is discussing with a patient, a 60-year-old man with atherosclerotic large vessel disease, his potential enrollment in a phase 2 trial on a new antithrombotic drug compared to aspirin. According to the principle of equipoise, which of the following should the neurologist discuss with the patient?

A. Exactly half of recruited patients will receive the experimental drug, and half will receive aspirin
B. The investigator will cover 50% of the patient's expenses stemming from the trial
C. It is uncertain whether the tested drug is more effective than aspirin
D. The tested drug is expected to have at least 50% fewer side effects than aspirin
E. The tested drug is likely to be at least 50% as efficacious as aspirin

▶ **18.** A 70-year-old man with a history of coronary artery disease and myocardial infarction 2 years ago is brought to the emergency department within 30 minutes of acute-onset right-sided weakness and speech difficulties. Evaluation within 15 minutes of arrival reveals dense right hemiparesis and aphasia. Blood pressure is 170/95 mm Hg. A CT is obtained within 20 minutes and shows an effacement of the gray-white matter junctions near the left insula and lenticular nucleus. EKG, cardiac enzymes, oxygen saturation, blood glucose, electrolytes, and platelet count test results are normal. The results of prothrombin time and activated partial thromboplastin time are pending. The patient has no history of receiving oral anticoagulants or heparin, known liver disease, bleeding disorder, previous head trauma, stroke, cerebral hemorrhage, gastrointestinal or urinary hemorrhage, recent arterial puncture, or seizures. Current medications include lisinopril, atorvastatin, and aspirin. What is the recommended approach regarding treatment with IV recombinant tissue-type plasminogen activator (rt-PCA) in this patient?

A. Administer rt-PA as soon as possible, and no later than 60 minutes of emergency department arrival
B. Await the results of coagulation studies before administering tissue plasminogen activator
C. Do not administer rt-PA in this patient since he has been taking aspirin
D. Obtain written informed consent, given the risk posed by the patient's age and cardiac comorbidity
E. Reduce arterial blood pressure to about 150/85 mm Hg to reduce risk of intracerebral hemorrhage

▶ **19.** A 56-year-old right-handed man is evaluated for acute onset of right hemiplegia and aphasia 2 hours ago. A CT scan of the head shows loss of gray-white matter differentiation in the left insular cortex and a hyperdense left middle cerebral artery sign. Which of the following mechanisms is primarily responsible for neuronal loss in the ischemic core in this hypoperfused area at this time?

A. Accumulation of intracellular calcium
B Activation of caspases
C. Efflux of sodium from neurons
D. Increased glutamate uptake by astrocytes
E. Permanent hyperpolarization

▶ **20.** A 62-year-old man is seen by the acute stroke intervention team after he is brought to the emergency department by a neighbor who found him alone and "confused." The onset of the event was not witnessed. Examination reveals right hemiparesis and aphasia. A noncontrast CT is performed. Which of the following findings would represent a contraindication for thrombolytic therapy?

A. A clearly delineated hypodense lesion in the left middle cerebral artery territory
B. Hyperdense left middle cerebral artery sign
C. Loss of gray-white matter differentiation in the left insular cortex
D. Loss of gray-white matter differentiation in the left lentiform nucleus
E. Sulcal effacement in the left hemisphere

▶ **21.** A 44-year-old right-handed woman with no previous history of stroke is found by her husband on the floor at home in the evening. She has paralysis of the right side of the body and is unable to understand or talk. She was normal when he left her to go to work early that morning. Upon evaluation at the emergency department, she has a severe dense hemiplegia, global aphasia, and gaze preference to the left. A CT scan of the head performed within 20 minutes of arrival shows a hyperdense left middle cerebral artery (MCA) sign and hypodensity involving greater than 50% of the MCA territory. She is admitted to the stroke unit for optimal management of blood pressure, airway, and other parameters. Two days after admission, she becomes increasingly somnolent and eventually comatose. Which of the following is the most likely cause of her neurologic deterioration?

A. Aspiration pneumonia
B. Cerebral edema
C. Hemorrhagic transformation
D. Progressing ischemia
E. Status epilepticus

▶ **22.** A 66-year-old woman with a history of hypertension is brought to the emergency department at 8:00 AM because she awoke with acute onset of left-sided weakness in the left side of the body 1 hour before. According to the patient and her husband, she was normal when she went to bed at 9:00 PM the previous night. Evaluation on arrival reveals a left hemiparesis and dysarthria. Blood pressure is 175/100 mm Hg. A CT scan shows early ischemic changes in the right insula and lenticular nucleus. EKG, cardiac enzymes, blood glucose, platelet count, prothrombin time, and activated partial thromboplastin time are normal. Which of the following is the most appropriate treatment for this patient according to current guidelines?

A. Aspirin
B. Heparin
C. Intraarterial recombinant tissue-type plasminogen activator
D. IV recombinant tissue-type plasminogen activator
E. Labetalol

23. In a recent prospective study of 300 patients with suspected strokes conducted in an urban teaching hospital, about one-third of patients were ultimately diagnosed with stroke mimics. Which of the following factors correlated most strongly with an ultimate accurate diagnosis of stroke?

A. Age over 55
B. Concurrent headache
C. History of focal neurologic symptoms
D. History of prior stroke
E. Normal metabolic profile in the emergency department

24. A 60-year-old right-handed woman is evaluated for acute onset of left arm and face weakness 2 hours ago. She has a history of hypertension that is well controlled with hydrochlorothiazide. At the time of her evaluation in the emergency department, her left arm weakness had improved slightly. She was found to have a blood pressure reading of 160/100 mm Hg, and she was treated with labetalol, resulting in a reduction of blood pressure to her basal levels of 140/90 mm Hg. A few minutes later, however, her weakness worsened, resulting in left hemiplegia. Which of the following mechanisms is most likely to explain the neurologic deterioration in this patient?

A. Hemorrhagic transformation
B. Ischemic vasoconstriction
C. Loss of autoregulation
D. Neuronal hyperpolarization
E. Vasogenic edema

25. Very early initiation of neuroprotective therapies is one approach being investigated for preservation of the penumbra in early stroke. Which of the following factors places the greatest limitation on the development and evaluation of potential neuroprotective therapies?

A. Many patients will ultimately have stroke mimics
B. Many therapies cannot be given during prehospital transport
C. Many therapies may conflict with common medications
D. Most patients are treated too late to help
E. Neuroprotective agents are not profitable for pharmaceutical companies

26. The recent Joint Commission stroke-specific care performance measures include which of the following treatment requirements?

A. Discharge on a cholesterol-lowering medication
B. Discharge on an angiotensin-converting enzyme inhibitor
C. Screen for dysarthria
D. Start antithrombotic therapy by the end of the first week of hospitalization
E. Start antithrombotic therapy within 2 months of discharge

27. A 35-year-old woman is evaluated because she noticed that she became acutely unable to read the newspaper 2 hours ago. On examination she is alert and oriented and has no focal weakness. She is able to write a simple

sentence on dictation but is unable to read it. This is most likely due to an infarction in which of the following vascular territories?

A. Left lenticulostriate
B. Left middle cerebral
C. Left posterior cerebral
D. Right middle cerebral
E. Right posterior cerebral

▶ **28.** Which of the following is the objective of a phase 2 clinical trial on a new drug?

A. To assess bioavailability of the drug in the target tissue
B. To determine how the drug is working in the "real world," both in terms of efficacy and safety, after US Food and Drug Administration (USFDA) approval
C. To determine whether the drug produces toxic effects on experimental animals
D. To obtain comparative information about relative safety and efficacy of the drug in a randomized controlled trial (RCT)
E. To obtain, in an RCT, definite data on the drug's benefits and risks based on promising results from previous RCTs

▶ **29.** Which of the following interventions is recommended as a first-line treatment for controlling hypertension *after* the administration of recombinant tissue-type plasminogen activator?

A. Bolused, then infused, labetalol
B. Infused IV clonidine
C. Infused IV nimodipine
D. IV sodium nitroprusside drip
E. Nitropaste

▶ **30.** In order to develop a successful primary stroke center, the authors of the chapter "Primary Stroke Center Certification" outline numerous resources that should be made available and requirements that should be met. In order to ensure improved patient outcomes, which of the following is continually emphasized by the authors?

A. Admission orders should be tailored to the individual patient
B. Constant documentation and logbooks must be kept
C. Emergency department personnel should defer to neurologists for stroke management
D. A stroke center is best led by a group of physicians
E. The stroke team should respond within 1 hour of being notified

▶ **31.** A 70-year-old man is brought to the emergency department 1 hour after the onset of difficulty speaking and right-hand clumsiness. He has a history of coronary artery disease, type 2 diabetes mellitus, hypertension, and hyperlipidemia. He underwent coronary artery bypass grafting 2 years ago and a cystoscopy 3 weeks ago. One year ago, a small thalamic hemorrhage was found after he underwent a head CT done after a confusional episode.

On examination, he is alert. Blood pressure is 170/90 mm Hg, and heart rate 55 beats per minute. Language is nonfluent with difficulty naming and repeating as well as with writing. Comprehension is generally preserved. Right upper extremity pronator drift and difficulty with fine motor movements in the right hand are present. A noncontrast CT of the brain is normal. The treating physicians are considering the use of recombinant tissue-type plasminogen activator (rt-PA). Which of the following excludes the use of rt-PA in this patient?

A. Elevated blood pressure
B. Inability to give informed consent
C. Prior coronary artery bypass grafting
D. Prior intracranial hemorrhage
E. The recent urologic procedure

▶ **32.** A group of researchers begins to recruit patients for an acute stroke trial involving a medication designed to limit the area of infarct in cortical strokes. The medication used has shown promising results in phase 2 trials involving small numbers of patients. After 6 months, the number of patients recruited falls 30% short of the target. Some of the investigators suggest changing the protocol to include subcortical strokes. According to the authors of the chapter "'How To' Guide for Clinicians Interested in Becoming Involved in Clinical Stroke Research," what is a potential drawback of this strategy?

A. The drug may not work for a different pathophysiology
B. The investigators will appear to be motivated by personal gain
C. It may be unethical to change the rules midway through the trial
D. The mechanism of action may not be understood
E. There is potential to harm those recruited under new criteria

▶ **33.** Deep venous thrombosis (DVT) is a well-recognized severe complication of acute ischemic stroke. The authors of the chapter "Complications of Ischemic Stroke: Prevention and Management" discuss the Prevention of Venous Thromboembolism After Acute Ischaemic Stroke (PREVAIL) trial, designed to determine the optimal anticoagulant for use in prevention of poststroke DVT. They note, however, that despite the fact that the PREVAIL trial was well designed, its efficacy and safety end points failed to determine whether enoxaparin (low-molecular-weight heparin) or unfractionated heparin was a better treatment. Which of the following statements summarizes the results of this trial?

A. Enoxaparin was less safe and less effective.
B. Enoxaparin was safer but less effective.
C. Results were indeterminate.
D. Unfractionated heparin was less safe and less effective.
E. Unfractionated heparin was safer but less effective.

▶ **34.** A 46-year-old right-handed woman is evaluated for acute onset of left hemiplegia and sensory loss. A CT scan of the head shows loss of gray-white matter differentiation in the right middle cerebral artery territory.

Which of the following mechanisms may reduce NMDA-mediated excitotoxic neuronal loss in this area?

A. Activation of matrix metalloproteinases
B. Calcium release from the endoplasmic reticulum
C. Extracellular acidosis
D. Inhibition of glutamate transport by astrocytes
E. Neuronal depolarization

▶ **35.** A 62-year-old man with a history of hypertension and hypercholesterolemia treated with lisinopril, atorvastatin, hydrochlorothiazide, and aspirin is brought to the emergency department at 60 minutes after acute-onset left-sided weakness. Evaluation upon arrival reveals a left hemiparesis and dysarthria. Blood pressure is 160/90 mm Hg. A CT scan shows early ischemic changes in the right insula. EKG, cardiac enzymes, blood glucose, platelet count, prothrombin time, and activated partial thromboplastin time test results are normal. The patient has no history of head trauma, stroke, hemorrhage, or recent surgeries or arterial punctures. Which of the following is a potential risk of IV recombinant tissue-type plasminogen activator (rt-PA) in this patient?

A. Angioedema
B. Hyponatremia
C. Myonecrosis
D. Rash
E. Seizures

▶ **36.** According to the authors of the chapter "'How To' Guide for Clinicians Interested in Becoming Involved in Clinical Stroke Research," which of the following criteria should be met before entering patients into clinical trials?

A. The different phases of clinical trials should be explained to patients
B. Expenses related to the trial are the patient's responsibility
C. Free drug should be given if the trial is successful
D. Patients must agree to complete the trial
E. The trial must have a placebo arm

▶ **37.** A 56-year-old right-handed woman is evaluated for acute onset of left hemiplegia 2 hours ago. A CT scan of the head shows loss of gray-white matter differentiation in the left insular cortex and basal ganglia. There is an area of diffusion-weighted imaging (DWI)/perfusion-weighted imaging (PWI) mismatch on MRI. Which of the following statements best describes the area of ischemic penumbra in this case?

A. The area of penumbra includes neurons that are at risk of undergoing apoptosis.
B. The cerebral blood flow in the area of ischemic penumbra is typically less than 7 mL/100 g/min.
C. The DWI abnormalities correspond to a core that remains unchanged with the duration of ischemia.
D. The DWI abnormalities precisely delineate the area of irreversible cell damage.
E. The DWI abnormality represents areas of increased permeability of the blood-brain barrier.

▶ **38.** A 65-year-old man with a history of hypertension, hyperlipidemia and type 2 diabetes mellitus notes the acute onset of unsteadiness with inability to walk 30 minutes after returning from the golf course. He is mildly nauseated but does not have vertigo. His glucometer reading at home is 130. He is taken by ambulance to an emergency department (ED) where he is examined by an ED resident 90 minutes after the onset of his symptoms. Vital signs show a blood pressure of 170/90 mm HG and are otherwise normal, as is his blood sugar. Further examination shows gaze-evoked nystagmus with mildly slurred speech. Finger-to-nose and heel-to-shin testing are fairly unremarkable. The NIH Stroke Scale (NIHSS) score is 1. He stands with assistance but is completely unable to walk, listing to the left. The radiology department calls to report an abnormal diffusion-weighted imaging reading on MRI. What is the most likely explanation for the inconsistency between the clinical findings and the NIHSS score?

A. Dysarthria is not a component of the scale
B. It was performed by a non-neurologist
C. It was performed too acutely
D. The NIHSS does not provide a comprehensive neurologic assessment
E. The patient probably did not have a stroke

▶ **39.** In the Interventional Management of Stroke I and II pilot studies, reduced-dose IV recombinant tissue-type plasminogen activator (rt-PA) was combined with intraarterial rt-PA delivered either by microcatheter or an EKOS MicroLysus® Ultrasound Catheter. Approximately what additional percentage of patients achieved distal perfusion when intraarterial methods were combined with IV treatment?

A. No advantage to combined therapy
B. 10%
C. 25%
D. 60%
E. 100%

▶ **40.** An 80-year-old man is admitted to a hospital stroke unit 2 hours after awakening with right-sided weakness and slurred speech. He is not treated with thrombolytic therapy and is placed on aspirin. He is initially alert and able to communicate, although he has "thick" speech. He walks with assistance. On the second hospital day, staff notes that he is now weaker on the right side and unable to ambulate to the bathroom. He is afebrile and alert with normal laboratory values. Statistically, according to a large study cited by the authors of the chapter "Complications of Ischemic Stroke: Prevention and Management," what is the most likely reason for deterioration in this patient's neurologic status?

A. Hemorrhagic conversion
B. Hydrocephalus
C. Increased intracranial pressure
D. A new, second stroke
E. Progression of the stroke

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PATIENT MANAGEMENT PROBLEM

Rishi Gupta, Joshua M. Levine

The following patient management problem was chosen to reinforce the subject matter presented in this issue. It emphasizes decisions facing the practicing physician. At each decision point determine how you, as the neurologist, would respond. Then answer the questions provided. The weight or "value" indicates the relative strength or weakness of the response as determined by the faculty. Use these values, as well as the critical comments, to assess your own understanding and handling of the problem. A review of all responses, not merely the ones you select, is recommended.

Educational Objective

▶ Neurologists are often consulted in the treatment of acute ischemic stroke. This patient management problem helps to reinforce the key issues neurologists face in the emergency department at the time of an acute ischemic stroke and helps to address some of the practical patient management issues that may occur.

Case History

▶ A 75-year-old man with a history of hypertension and atrial fibrillation presents to the emergency department 90 minutes from last being seen normal with a left gaze deviation, global aphasia, and right-sided hemiplegia. At the time of arrival to the emergency department, his NIH Stroke Scale (NIHSS) score is 24.

Past medical/social history. The patient had been scheduled for a colonoscopy to be performed in 2 days and had held the last dose of his warfarin in preparation for the procedure. He is accompanied by his wife, who confirms the time of onset.

Evaluation. In the emergency department, blood work is sent for basic chemistries, coagulation profile, and complete blood counts. The patient is en route to the CT scanner.

Decision Point A. Based on the above information, what should be the next step in the management of this patient?

A1. Examine the patient prior to the CT scan of the brain
A2. Obtain more history from his wife

Relationship Disclosure: Dr Gupta has received personal compensation for activities with Concentric Medical, Inc. Dr Levine has nothing to disclose. *Unlabeled Use of Products/Investigational Use Disclosure:* Drs Gupta and Levine have nothing to disclose.

A3. Add a CT angiogram to the noncontrast CT of the brain
A4. Have the emergency department staff ensure that alteplase is at the bedside
A5. Obtain results of the blood work and vital signs

The patient undergoes CT of the brain without contrast, which reveals no evidence of an intracranial hemorrhage and no evidence of early ischemic changes. A CT angiogram reveals the presence of a left carotid terminus occlusion. The patient has normal laboratory blood work except for an international normalized ratio (INR) of 1.5. The neurologist speaks with the wife, who reports the patient has no history of surgical procedures. His blood pressure is 190/100 mm Hg. A neurologic examination confirms his NIHSS score of 24, and the patient is now 120 minutes from symptom onset.

Decision Point B. What treatments are warranted at this point?

B1. IV alteplase total 0.9 mg/kg with a 10% bolus and the rest over 1 hour
B2. IV labetalol 10 mg to lower the blood pressure
B3. IV alteplase total 0.6 mg/kg with a 15% bolus and then call interventionist for intraarterial thrombolysis
B4. No IV therapy; call interventionist for intraarterial thrombolysis
B5. No therapy, as patient has an INR of 1.5

One dose of IV labetalol is administered, and the blood pressure is reduced to 160/80 mm Hg. The glucose level is noted to be 200 mg/dL. The patient weighs 120 kg and is given a bolus of 9 mg of alteplase; an infusion of 81 mg is given over 1 hour. The patient shows no neurologic improvement after 60 minutes and is noted to have an NIHSS score of 24.

Decision Point C. What are the options for the next step in the management of this patient?

C1. Admit to the neurointensive care unit for further observation
C2. Call interventionist and offer patient intraarterial therapy
C3. Carefully monitor glucose level
C4. Allow blood pressure to rise to help perfusion to the brain

The patient is admitted to the neurointensive care unit, and a sliding scale insulin protocol is initiated to help bring the glucose level to below 150 mg/dL. The patient shows little clinical improvement after 24 hours.

Decision Point D. What should be the next management step for the patient?

D1. Start a heparin drip, given that atrial fibrillation is the cause of the stroke
D2. Obtain a CT of the brain to assess for hemorrhagic conversion
D3. Obtain an MRI of the brain to assess for extent of injury
D4. Consult a neurosurgeon for a hemicraniectomy

WEIGHTS AND COMMENTS

EXPLANATION OF WEIGHTS:

+5 Unequivocally required for diagnosis or effective treatment, without which management would be negligent

+3 Important for diagnosis and treatment but not immediately necessary

+1 Potentially useful for diagnosis and treatment (routine studies fall into this category)

0 Neutral impact, neither clearly helpful nor harmful under given circumstances

–1 Not harmful, but nonproductive, time-consuming, and not cost-effective

–3 Nonproductive and potentially harmful

–5 Totally inappropriate and definitely harmful; may threaten life

A1. Examine the patient prior to the CT scan of the brain +3

It is important in the setting of an acute ischemic stroke to have a system in place to increase efficiency. If the patient is already en route for a CT scan, this time may be used to obtain more history, clarify the time of onset, and gather pertinent information about surgical history in order to determine if the patient is suitable for IV alteplase. Once the patient has returned, it is important to perform a thorough examination that, along with the NIHSS score, will help to determine the severity of the clinical deficit.

A2. Obtain more history from his wife +3

If the patient's family member is not at the bedside to corroborate the history, it is helpful to attempt to contact witnesses. The emergency medical services (EMS) team generally records contact information for witnesses or next of kin. Sometimes the time of onset can only be determined from the EMS team's discussion with witnesses at the scene. If ambiguity exists about the clinical history, phone calls can help clarify matters.

A3. Add a CT angiogram to the noncontrast CT of the brain +1

CT angiography is being increasingly used at institutions to assess for a large artery occlusion at the time of clinical presentation. This test requires placement of an 18-gauge IV into the antecubital vein and may sometimes delay the noncontrast head CT. For a patient within the window for IV alteplase therapy, a noncontrast head CT is the only test required to decide whether the therapy is warranted.

A4. Have the emergency department staff ensure that alteplase is at the bedside +5

Many institutions have implemented a "clot box" that is available in the emergency department for patients with acute ischemic stroke. It is helpful to notify the emergency department nurse to have alteplase available at the bedside at the time of examination and while the patient is undergoing a CT scan. Delays can occur if the medication is not available at the bedside when a decision has been made to proceed with treatment. This step ensures efficiency and avoids time delays for administration of alteplase.

A5. Obtain results of the blood work and vital signs +5

The results of the blood work are crucial as there are laboratory values that may exclude this patient from treatment with IV alteplase. A glucose level less than 50 mg/dL or greater than 400 mg/dL, a platelet count less than 100,000, or an INR greater than 1.7 are considered relative contraindications for administration of the medication. The blood pressure is important to monitor as blood pressure elevation has been linked to hemorrhagic conversion after alteplase administration.

B1. IV alteplase total 0.9 mg/kg with a 10% bolus and the rest over 1 hour –3

The patient has a contraindication to the administration of the medication with an elevated blood pressure of 190/100 mm Hg. Prior to treatment with thrombolysis, the blood pressure should be reduced to less than 185/110 mm Hg.

B2. IV labetalol 10 mg to lower the blood pressure +5

Administration of IV antihypertensive medications can be performed prior to treatment with thrombolysis. A total of three doses of IV labetalol can be attempted. If a patient requires a continuous infusion of antihypertensive medication, then treatment with IV thrombolysis is contraindicated.

B3. IV alteplase total 0.6 mg/kg with a 15% bolus and then call interventionist for intraarterial thrombolysis 0

This treatment modality is currently being investigated as part of a phase 3 clinical trial in which patients are randomized to treatment with standard IV alteplase (0.9 mg/kg total dose) and compared with patients treated with two-thirds of the dose followed by intraarterial delivery of thrombolytics. The results of this study will aid in answering this important question for patients with large vessel occlusions.

B4. No IV therapy; call interventionist for intraarterial thrombolysis 0

Patients with exclusions to IV thrombolysis, such as recent surgery, or elevated INRs can be considered for mechanical or pharmacologic treatment with intraarterial therapy. In the example given, the patient's blood pressure was lowered with one dose of labetalol, and he has no exclusions to IV thrombolysis. The patient should be considered for IV thrombolysis first.

B5. No therapy, as patient has an INR of 1.5 –3

An INR level greater than 1.7 is an exclusion for IV alteplase. This patient had an INR of 1.5, which should not exclude him from consideration for therapy.

C1. Admit to the neurointensive care unit for further observation +3

Patients who have been treated with IV thrombolytics should be admitted to a unit that allows for careful neurologic assessments along with careful monitoring of blood pressure and glucose. Patients admitted to neurointensive care units are found to have better clinical outcomes when compared to general medical and surgical intensive care units for the diagnosis of ischemic stroke. After administration of thrombolytics, patients should not be placed on anticoagulation therapy for at least 24 hours.

C2. Call the interventionist and offer patient intraarterial therapy +1

Patients who have a persistent large vessel occlusion after administration of IV alteplase may be candidates for rescue therapy with endovascular approaches. It is hoped that the ongoing Interventional Management of Stroke Trial III (IMS III) will address the question of efficacy of combined IV plus intraarterial therapy versus IV therapy alone. Studies have shown that the recanalization rate of thrombus after administration of IV alteplase is dependent on the location of the thrombus. Clots in more proximal locations (ie, carotid terminus) have a lower recanalization rate compared with distal middle cerebral artery branches. On a case-by-case basis, consideration can be given to endovascular therapy for such clinical situations until data from the randomized controlled study become available.

C3. Carefully monitor glucose level +3

Recent evidence suggests that hyperglycemia is linked with higher rates of intracranial hemorrhage after administration of thrombolytics. In patients with elevated glucose levels, it may be of benefit to treat and carefully monitor glucose levels, but it is important to avoid hypoglycemia as this may be more detrimental. Ongoing studies are determining whether insulin drip protocols lead to improved outcomes in patients who have suffered an acute ischemic stroke, and they may help to guide how aggressively glucose should be controlled in the acute setting.

C4. Allow blood pressure to rise to help perfusion to the brain 0

Studies suggest that in the setting of a large vessel occlusion, induced hypertension may help to reduce clinical deficits by improving perfusion to the tissue. For patients receiving thrombolytics, keeping the blood pressure below 185/110 mm Hg aids in reducing the risk of hemorrhage. For the patient in the clinical scenario presented, aggressively lowering the blood pressure too quickly may be harmful, while targeting a blood pressure above normotensive may be more beneficial.

D1. Start a heparin drip, given that atrial fibrillation is the cause of the stroke −3

The patient is now 24 hours from administration of alteplase, but no imaging study has been performed to determine the size of the infarct or whether hemorrhage is present. Hemorrhage, particularly petechial hemorrhage, may be clinically asymptomatic in patients with large strokes. Because there is concern for a large infarct based on the clinical examination, heparin at this time point may place the patient at a high risk for hemorrhagic transformation. Given that the risk of stroke from atrial fibrillation is 6% per year, the day-to-day risk is relatively low and probably does not justify the risk of hemorrhage that would be associated with the use of heparin at this time.

D2. Obtain a CT of the brain to assess for hemorrhagic conversion +3

A CT scan 24 hours after thrombolysis allows the clinician to identify the extent of injury in this instance as well as assess for early signs of edema, particularly given the concern for a large infarct. If hemorrhage is present, it is important to discuss the prognosis as well as the goals of therapy with the family. Patients with large infarcts

and global aphasia with right-sided weakness may require a feeding tube for nutrition and will likely suffer significant disability, and the family will need education about caring for the patient.

D3. Obtain an MRI of the brain to assess for extent of injury 0

An MRI of the brain can help to define the severity of the brain injury on diffusion-weighted maps early in the stroke course. In the current clinical scenario, a noncontrast CT 24 to 48 hours after admission can often give the same degree of information. Evidence of a large infarct on diffusion-weighted maps on MRI may help the clinician decide which patients are at high risk for malignant cerebral edema and brain herniation from a massive stroke.

D4. Consult a neurosurgeon for a hemicraniectomy 0

Given the age of the patient and the fact that the clinical deficit is in the left hemisphere, hemicraniectomy may be a lifesaving measure but will not help to reduce the clinical deficit. Recent studies have shown that younger patients appear to derive the most benefit from such procedures and that older patients are often left with significant disability and full dependence of care. No randomized controlled study has been completed to date to help address this question. Several studies were initiated, but none was completed.

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PREFERRED RESPONSES

Following are the preferred responses and critiques for the multiple-choice items in this CONTINUUM issue. The questions and answer selections are repeated, and the preferred response appears in bold print. In most cases, this is followed by an explanation and, in some instances, a reference with which you may seek more specific information. No score will be assigned to the answer form you mail in, since the emphasis of this program is on self-assessment. You are encouraged to review the responses and explanations carefully to evaluate your general understanding of the course material.

TYPE A QUESTIONS (ONE BEST ANSWER)

▶ **1.** An intraaortic balloon device that produces partial obstruction to aortic blood flow has been tested in small pilot studies as a therapy to improve stroke outcome. What is the guiding principle behind the use of such a device after stroke?

A. It disrupts cerebral autoregulation
B. It increases blood flow to the brain
C. It prevents further cerebral emboli
D. It prevents platelet aggregation
E. It raises systemic blood pressure

The correct answer is B. This device has been shown in small pilot studies to redirect systemic blood flow to the brain with the goal of increasing collateral circulation to the ischemic penumbra. In one case series of 16 patients cited by the authors, no resulting increase in systemic blood pressure was shown. Another approach to increasing collateral circulation after stroke would be to induce systemic hypertension pharmacologically. The authors of the chapter "Emerging Therapies" report that these therapies may prove of some value as "bridging therapies" until occluded vessels can be recanalized.

▶ **2.** A 70-year-old woman with a history of hypertension and type 2 diabetes is admitted to the hospital 1 hour after the acute onset of inability to move the left side. On admission, she has a left hemiparesis, greater in the arm than leg, and hemispatial neglect. MRI with diffusion-weighted imaging demonstrates an acute right middle cerebral artery infarct, and recombinant tissue-type plasminogen activator (rt-PA) is administered without complication. The stroke team is concerned about her inability to move the left leg well. If the follow-up head CT shows no intracranial

hemorrhage, how long after administration of rt-PA should the team wait before initiating deep venous thrombosis prophylaxis with anticoagulants?

A. 24 Hours
B. 3 to 4 Days
C. 7 to 10 Days
D. Contraindicated
E. Not contraindicated, but not useful

The correct answer is A. The authors of the chapter "Complications of Ischemic Stroke: Prevention and Management" state that anticoagulants for prevention of deep venous thrombosis (DVT) in ischemic stroke can be initiated 24 hours after rt-PA therapy. Antiembolic stockings and pneumatic compression devices can be used safely in the immediate postthrombolysis period for DVT prophylaxis. In intracranial hemorrhage (obviously without use of rt-PA), no definitive information is available, but 3 to 4 days postevent is suggested. There is no contraindication to the use of anticoagulants in doses used to prevent DVT after 24 hours from the use of thrombolytic therapy, nor has evidence been presented that they are not useful.

▶ **3.** A 47-year-old man is evaluated for acute onset of right hemiplegia. The MRI of the head shows an area of diffusion-weighted imaging/perfusion-weighted imaging mismatch on MRI. Which of the following mechanisms primarily leads to cell death in the jeopardized area of penumbra in this case?

A. Caspase-triggered nuclear fragmentation
B. Closure of mitochondrial permeability transition pore
C. Decreased expression of endothelial cell adhesion molecules
D. Phospholipase-induced membrane destruction
E. Total depletion of mitochondrial-produced adenosine-5′-triphosphate

The correct answer is A. Cell death in the area of ischemic penumbra primarily involves a mechanism of apoptosis. This process depends on activation of caspases in response to cytochrome *c* release from mitochondria into the cytoplasm via a permeability transition pore. Caspase activation requires a residual reserve of adenosine triphosphate and triggers fragmentation of nuclear DNA. Apoptosis does not trigger inflammation, which typically occurs in areas of necrosis in response to release of intracellular contents following plasma membrane fragmentation by action of calcium-activated phospholipases, oxidative stress, and other factors.

▶ **4.** 70-year-old man with a history of hypertension and hyperlipidemia is transported within 30 minutes of the onset of acute inability to move his left side from a rural area to a hospital that is a designated primary stroke center. He is assessed by emergency medical services personnel in the field and by an emergency department physician on arrival. According to the authors of the chapter "Primary Stroke Center Certification," which of the following aspects of primary stroke center care may lead to a better outcome for this patient?

A. Any place that treats more strokes will be better at it
B. Experimental protocols can be used for difficult cases

C. The patient is more likely to receive recombinant tissue-type plasminogen activator
D. Physician reimbursement is better, so specialists are more likely to come in
E. Treatment is more conservative and less likely to produce morbidity

The correct answer is C. Many reasons are put forth by the authors of the chapter "Primary Stroke Center Certification" to argue for expansion and emphasis on developing primary stroke care centers with the goal of improved patient outcomes from stroke, including those that have to do with standardization of stroke care, continuing education of staff, and continuous data analysis. Stroke neurologists have worked for better reimbursement of acute stroke care rendered by physicians, but thus far this reimbursement is not exclusive to designated centers. Treatment is likely to be more aggressive and less conservative—ie, patients are more likely to receive recombinant tissue-type plasminogen activator, which, per several studies cited in the text, shows improved patient outcome at 1 year. The authors imply that treating a lot of strokes without following standardized protocols does not offer an advantage to patients; experimental protocols may be available in some primary stroke care centers, but their effect on outcomes may be unknown.

Kwiatkowski TG, Libman RB, Frankel M, et al. Effects of tissue plasminogen activator for acute ischemic stroke at one year. National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study Group. N Engl J Med 1999;340(23):1781–787.

▶ **5.** A 55-year-old man is seen by the acute stroke intervention team 2 hours after acute onset of right-sided weakness and aphasia. Should this patient be eligible for treatment with tissue plasminogen activator (t-PA), which of the following tests should be conducted prior to initiating t-PA?

A. Arterial blood gases
B. Blood glucose
C. Chest x-ray
D. Liver function
E. Stool guaiac

The correct answer is B. In the acute stroke setting, blood glucose measurement can quickly exclude hypoglycemia or hyperglycemia as a potential stroke mimic. Cardiac enzymes and 12-lead EKG electrolytes, complete blood count, prothrombin time, activated plasma thromboplastin time, and renal function tests are recommended for all patients. In contrast, chest x-ray and stool guaiac test are not routinely recommended; arterial blood gases and liver function tests may be indicated in specific cases.

▶ **6.** A 62-year-old woman is brought to the emergency department within 30 minutes of acute-onset left-sided weakness. Evaluation within 15 minutes of arrival reveals dense left hemiparesis and left gaze preference. Blood pressure is 200/115 mm Hg. A CT shows effacement of the gray-white matter junction in the right insula. EKG, cardiac enzymes, oxygen saturation, blood glucose, electrolytes and platelet count, prothrombin time, and activated partial thromboplastin time test results are normal. The patient has

no history of previous head trauma or stroke; cerebral, gastrointestinal, or urinary hemorrhage; recent arterial puncture; or seizures. Which of the following drugs is recommended for treatment of hypertension before considering administration of IV recombinant tissue-type plasminogen activator (rt-PCA) in this patient?

A. Clonidine
B. Enalapril
C. Hydralazine
D. Labetalol
E. Nifedipine

The correct answer is D. If the patient is eligible for treatment with IV rt-PA but the systolic blood pressure is greater than 185 mm Hg or the diastolic blood pressure is greater than 110 mm Hg, antihypertensive treatment should be initiated to reduce the risk of hemorrhage. Drugs recommended include IV labetalol or nicardipine infusion.

▶ **7.** In addition to the fact that timing of final assessments in stroke trials is not standardized, the authors of the chapter "'How To' Guide for Clinicians Interested in Becoming Involved in Clinical Stroke Research" state that there is little agreement on the best outcome measures to be used in acute stroke trials. Which of the following outcome measures is felt to be the most meaningful according to the authors?

A. Impairment measures
B. Measures of activity
C. Percent of brain tissue damaged
D. Prevention of future strokes
E. Quality-of-life questionnaires

The correct answer is B. The authors of the chapter "'How To' Guide for Clinicians Interested in Becoming Involved in Clinical Stroke Research" state that both the optimal timing of assessments poststroke and the outcome measures used in various trials have hardly been standardized and make cross-trial comparisons difficult. They feel that while objective measures such as percent of brain tissue damaged and other ratings, such as those in impairment measures and quality-of-life questionnaires, are important, they are probably less meaningful overall than measures of activity that patients are able to resume. Additionally, the authors note that even when common scales to measure activity (eg, the Modified Rankin Scale) are used, cutoff points differ among trials.

▶ **8.** A group of neurologists servicing a large community hospital approach the board of directors and express their desire to organize a dedicated stroke unit. They provide information to the board that shows that functional outcomes in stroke units are superior and that benefits to patients are lasting. Which of the following is the most likely explanation for the improved outcomes in certified stroke units?

A. Availability of interventional radiology
B. Better nursing to patient ratio
C. Better prevention and treatment of infections

D. Higher profits increase future unit funding
E. Inclusion of rehabilitation services

The correct answer is C. The authors of the chapter "Complications of Ischemic Stroke: Prevention and Management" note that disease-specific care in a dedicated stroke unit of a hospital results in reduced stroke mortality, better functional outcomes, and lowered costs. They cite a paper by Govan and colleagues (2007) and note that the likely reason for better outcomes is a reduction in poststroke complications, particularly infections. While it may be true that stroke units lower costs and that they include multidisciplinary teams (rehabilitation, interventional radiology, skilled nursing staff), it is the prevention and early treatment of stroke-related complications (particularly infections) that account for better outcomes.

Govan L, Langhorne P, Weir CJ; Stroke Unit Trialists Collaboration. Does the prevention of complications explain the survival benefit of organized inpatient (stroke unit) care?: further analysis of a systematic review. Stroke 2007;38(9):2536–2540.

▶ **9.** The use of several imaging techniques for rapidly and accurately identifying the ischemic penumbra in patients with stroke is discussed by the authors of the chapter "Emerging Therapies." Which of the following suggests a large area of penumbra?

A. Distal middle cerebral artery occlusion
B. Early ischemic changes on CT
C. Lacunar infarction in the internal capsule
D. Large diffusion-weighted imaging abnormality
E. Large diffusion-weighted imaging/perfusion-weighted imaging mismatch

The correct answer is E. Several imaging techniques are already in use to better define the extent of the ischemic penumbra in patients with stroke so that a more precise strategy might be employed utilizing recanalization therapy outside the normal therapeutic windows. The authors of the chapter "Emerging Therapies" note that stroke is a very heterogeneous disease and that some patients may only have a small core of infarcted tissue even several hours out from their event. Early ischemic changes on CT can be seen in the core infarct; however, more information is needed (eg, from CT angiography) to try to calculate the area of the penumbra. A large diffusion-weighted imaging (DWI) abnormality suggests little salvageable tissue while a proximal (not distal) middle cerebral artery occlusion with a limited volume of early ischemic change suggests a large penumbra. Lacunar infarcts in strategic regions such as the internal capsule are difficult to evaluate in terms of distant effects on the penumbra. DWI/perfusion-weighted imaging mismatch implies that the infarcted core is relatively small while the area of perfusion deficit may be large and is reflective of the penumbra.

▶ **10.** A 75-year-old man with a history of atrial fibrillation treated with warfarin presents to an urgent care clinic because of inability to use his left hand since awakening that day. He reports no pain or numbness in the

hand but has been unable to raise his wrist. He states that he slept in his bed last night, although he has a tendency to doze off in his recliner. He is also treated with atenolol for mild hypertension. On examination, cognition is normal. Blood pressure is 130/80 mm Hg, and heart rate is irregular at 60 beats per minute. He is unable to extend the left wrist or fingers. Forearm extensors are normal. There is no sensory deficit along the dorsal thumb. He is sent home from the urgent care center and referred to a neurologist. The neurologist suspects a central lesion. Presence of which of the following signs or symptoms may alert the clinician to the possibility of stroke as a cause of distal arm weakness?

A. Gradual onset
B. Headache
C. Sensory symptoms
D. Stroke risk factors
E. Unilateral involvement

The correct answer is D. The authors of the chapter "Diagnosis of Stroke and Stroke Mimics in the Emergency Setting" cite a paper from Gass and colleagues (2001) describing 14 MRI-documented cases of distal arm (hand) weakness mimicking a peripheral nerve distribution but caused by small cortical strokes. Although abrupt onset—or rather onset after awakening—is a typical history given in peripheral palsies, certainly abrupt onset in an awake patient in an appropriate age group and with stroke risk factors should alert the clinician to the possibility of a central cause of hand/distal arm weakness. No mention is made of associated headache (unlikely, due to the small tissue volume of these strokes); sensory symptoms, although sometimes subjectively encountered in central lesions, are more likely to be found in a peripheral nerve lesion. Unilateral involvement is typical for either peripheral or central lesions. A history of prior strokes, while certainly possible, does not exclude a peripheral etiology.

Gass A, Szabo K, Behrens S, et al. A diffusion-weighted MRI study of acute ischemic distal arm paresis. Neurology 2001;57(9):1589–1594.

▶ **11.** A 75-year-old man is brought by ambulance to an emergency department (ED) 30 minutes after the acute onset of right-sided weakness and difficulty speaking. He is seen by an ED physician, and a noncontrast CT scan of the brain is normal. He is felt to be a candidate for recombinant tissue-type plasminogen activator (rt-PA) and receives a bolus of the drug. He is then accepted for transfer to a major university hospital. What is the current policy on reimbursement for rt-PA infusion as it relates to this patient?

A. The facility with the greatest number of hospital days for poststroke care can bill
B. The first hospital cannot bill for rt-PA because it provided only a bolus
C. The first hospital cannot bill for rt-PA because it was not given by a neurologist
D. The first hospital cannot bill if it is not a certified stroke center
E. The second hospital cannot bill for rt-PA because it was initiated in another facility

The correct answer is E. The authors of the chapter "Primary Stroke Center Certification" discuss the fact that reimbursement for administration of rt-PA has significantly improved under a new diagnosis related group (DRG) code (559); however, the facility that initiates the treatment is the only one that can bill for it. There is no current requirement for a neurologist to be present, nor is there a stipulation that rt-PA can only be given in a certified stroke center. Finally, choice A is cited as an irony in the current situation: the center that provides the most care may not, in fact, be able to bill for the drug if the patient has been transferred.

▶ **12.** A 56-year-old right-handed man is evaluated for acute onset of right hemiplegia and aphasia. A CT scan of the head shows loss of gray-white matter differentiation in the left insular cortex and basal ganglia and a hyperdense left middle cerebral artery sign. There is an area of diffusion-weighted imaging (DWI)/perfusion-weighted imaging mismatch on MRI, suggesting an area of penumbra in the left cerebral cortex. Which of the following mechanisms accounts for increased DWI signal in this patient?

A. Acute inflammation
B. Increased blood-brain barrier permeability
C. Intracellular edema
D. Luxury perfusion
E. Myelin breakdown

The correct answer is C. The increased DWI signal in the setting of cerebral ischemia represents restricted water diffusion (low apparent diffusion coefficient) that reflects intracellular (cytotoxic) edema.

▶ **13.** A 65-year-old man with new-onset atrial fibrillation is admitted to the hospital after awakening with right-sided weakness and difficulty producing the right word. He is diagnosed with an acute left middle cerebral artery infarct and placed in a step-down unit. Initial nursing assessment notes that he coughs when attempting to swallow water. Which of the following measures is most likely to be effective in preventing the development of pneumonia in this patient?

A. Daily pulmonary function tests
B. Formal swallowing evaluation
C. Prophylactic antibiotics
D. Transfer to an intensive care unit
E. Urgent percutaneous endoscopic gastrostomy placement

The correct answer is B. The authors of the chapter "Complications of Ischemic Stroke: Prevention and Management" note the severe impact caused by the development of pneumonia after acute stroke, as it both complicates the acute hospitalization and may prolong the recovery period. They note that the use of prophylactic antibiotics was not supported in a recent study, nor do they support immediate percutaneous endoscopic gastrostomy placement since many patients show improved swallowing function in the first few days. No evidence is presented that the patient's outcome will be better in an intensive care unit or with daily formal pulmonary assessment. However, the appropriate evaluation of swallowing

function with possible changes to oral diet based on the outcome is cited by the authors as a plausible measure to take to prevent pneumonia.

▶ **14.** Among the advantages of intraarterial delivery of fibrinolytic agents is the ability to deliver high concentrations of drug directly to the clot with less systemic exposure to the agent. However, widespread use of this technique is most likely to be limited because of which of the following factors?

A. High incidence of distal emboli
B. Lack of general availability of fibrinolytics
C. Lack of trained radiology personnel
D. Prohibitive liability costs
E. Specialized facilities and expertise required for neurointerventional treatment

The correct answer is E. The authors of the chapter "Emerging Therapies" note that intraarterial fibrinolytics have been used successfully in thrombolysis and definitely have a role in certain cases of large vessel occlusion. However, these procedures require trained interventional radiologists and angiography and, therefore, will most likely only be performed in tertiary care centers.

▶ **15.** A 72-year-old man with a history of hypercholesterolemia, hypertension, and an ST-elevation myocardial infarction 1 month ago is brought to the emergency department 60 minutes after acute-onset right-sided weakness and speech difficulties. Current medications include enalapril, atorvastatin, and aspirin. Evaluation reveals a right hemiparesis and global aphasia. Blood pressure is 170/100 mm Hg. A CT shows a hyperdense left middle cerebral artery and effacement of the gray-white matter boundary in the left insula. Cardiac enzymes, blood glucose, electrolytes, platelet counts, prothrombin time, and activated partial thromboplastin time are normal. Which of the following findings makes this patient ineligible for treatment with IV recombinant tissue-type plasminogen activator (rt-PA) according to current guidelines?

A. Aspirin use
B. Head CT scan findings
C. Hypertension
D. Recent myocardial infarction
E. Severity of neurologic deficit

The correct answer is D. According to the 2007 American Heart Association guidelines, eligibility criteria for IV rt-PA include no myocardial infarction in the previous 3 months. Although caution should be exercised when treating patients with major deficits, early ischemic changes that are not clear and do not affect multiple lobes or greater than one-third of the cerebral hemisphere should not preclude IV rt-PA in otherwise eligible patients. Age is not a contraindication for rt-PA treatment. Although the patient is hypertensive, his current blood pressure is less than 185 mm Hg systolic and less than 110 mm Hg diastolic and is therefore acceptable for treatment with IV rt-PA.

▶ **16.** At the beginning of 2008, the Joint Commission established 10 stroke-specific care performance measures as required for primary

stroke care center certification. Which of the following is included in that group of measures?

A. Anticoagulation for atrial fibrillation
B. Diabetes screening
C. Echocardiogram by day 2
D. Heparin for carotid artery disease
E. Repeat neuroimaging by day 2

The correct answer is A. While some of the above may be done in practice, per **Table 6-4**, anticoagulation for atrial fibrillation is correct.

▶ **17.** A neurologist is discussing with a patient, a 60-year-old man with atherosclerotic large vessel disease, his potential enrollment in a phase 2 trial on a new antithrombotic drug compared to aspirin. According to the principle of equipoise, which of the following should the neurologist discuss with the patient?

A. Exactly half of recruited patients will receive the experimental drug, and half will receive aspirin
B. The investigator will cover 50% of the patient's expenses stemming from the trial
C. It is uncertain whether the tested drug is more effective than aspirin
D. The tested drug is expected to have at least 50% fewer side effects than aspirin
E. The tested drug is likely to be at least 50% as efficacious as aspirin

The correct answer is C. Equipoise means that the physician expresses uncertainty toward which arm of a particular study is more effective.

▶ **18.** A 70-year-old man with a history of coronary artery disease and myocardial infarction 2 years ago is brought to the emergency department within 30 minutes of acute-onset right-sided weakness and speech difficulties. Evaluation within 15 minutes of arrival reveals dense right hemiparesis and aphasia. Blood pressure is 170/95 mm Hg. A CT is obtained within 20 minutes and shows an effacement of the gray-white matter junctions near the left insula and lenticular nucleus. EKG, cardiac enzymes, oxygen saturation, blood glucose, electrolytes, and platelet count test results are normal. The results of prothrombin time and activated partial thromboplastin time are pending. The patient has no history of receiving oral anticoagulants or heparin, known liver disease, bleeding disorder, previous head trauma, stroke, cerebral hemorrhage, gastrointestinal or urinary hemorrhage, recent arterial puncture, or seizures. Current medications include lisinopril, atorvastatin, and aspirin. What is the recommended approach regarding treatment with IV recombinant tissue-type plasminogen activator (rt-PCA) in this patient?

A. Administer rt-PA as soon as possible, and no later than 60 minutes of emergency department arrival
B. Await the results of coagulation studies before administering tissue plasminogen activator

C. Do not administer rt-PA in this patient since he has been taking aspirin
D. Obtain written informed consent, given the risk posed by the patient's age and cardiac comorbidity
E. Reduce arterial blood pressure to about 150/85 mm Hg to reduce risk of intracerebral hemorrhage

The correct answer is A. The National Institute of Neurological Disorders and Stroke recommends administration of IV rt-PA at 60 minutes from arrival in patients who are eligible according to current American Heart Association criteria. The patient has not been taking anticoagulants or received heparin in the previous 48 hours, has no clinical or CT evidence of bleeding, and has no previous conditions that may predispose to bleeding. Therefore, rt-PA can be administered even before results of the prothrombin time and activated partial thromboplastin time are available. Although the patient or family members should understand the potential risks and benefits of IV rt-PA treatment, informed consent is not required as IV rt-PA is considered standard of care.

▶ **19.** A 56-year-old right-handed man is evaluated for acute onset of right hemiplegia and aphasia 2 hours ago. A CT scan of the head shows loss of gray-white matter differentiation in the left insular cortex and a hyperdense left middle cerebral artery sign. Which of the following mechanisms is primarily responsible for neuronal loss in the ischemic core in this hypoperfused area at this time?

A. Accumulation of intracellular calcium
B. Activation of caspases
C. Efflux of sodium from neurons
D. Increased glutamate uptake by astrocytes
E. Permanent hyperpolarization

The correct answer is A. Cell death in the ischemic core typically occurs by a mechanism of necrosis. This is triggered by impaired adenosine triphosphate (ATP) production and disruption of ATP-dependent pumps, including the sodium/potassium adenosine triphosphatase. This results in accumulation of sodium in the cells (resulting in cytotoxic edema), impaired astrocyte reuptake of glutamate, and neuronal depolarization, which lead to massive influx of calcium both via glutamate- and voltage-gated calcium channels. Calcium activates phospholipases, nucleases, and proteases, leading to membrane destruction and cell death.

▶ **20.** A 62-year-old man is seen by the acute stroke intervention team after he is brought to the emergency department by a neighbor who found him alone and "confused." The onset of the event was not witnessed. Examination reveals right hemiparesis and aphasia. A noncontrast CT is performed. Which of the following findings would represent a contraindication for thrombolytic therapy?

A. A clearly delineated hypodense lesion in the left middle cerebral artery territory
B. Hyperdense left middle cerebral artery sign
C. Loss of gray-white matter differentiation in the left insular cortex

D. Loss of gray-white matter differentiation in the left lentiform nucleus
E. Sulcal effacement in the left hemisphere

The correct answer is A. The presence of an area of clearly delineated hypodensity with associated mass effect is indicative of established infarction and most likely inconsistent with a focal cerebral ischemia of less than 3 hours' evolution. Its presence is associated with increased risk of symptomatic intracerebral hemorrhage and constitutes a contraindication for thrombolysis.

▶ **21.** A 44-year-old right-handed woman with no previous history of stroke is found by her husband on the floor at home in the evening. She has paralysis of the right side of the body and is unable to understand or talk. She was normal when he left her to go to work early that morning. Upon evaluation at the emergency department, she has a severe dense hemiplegia, global aphasia, and gaze preference to the left. A CT scan of the head performed within 20 minutes of arrival shows a hyperdense left middle cerebral artery (MCA) sign and hypodensity involving greater than 50% of the MCA territory. She is admitted to the stroke unit for optimal management of blood pressure, airway, and other parameters. Two days after admission, she becomes increasingly somnolent and eventually comatose. Which of the following is the most likely cause of her neurologic deterioration?

A. Aspiration pneumonia
B. Cerebral edema
C. Hemorrhagic transformation
D. Progressing ischemia
E. Status epilepticus

The correct answer is B. The clinical examination and CT findings are significant clues. Although edema due to hemispheric infarction is relatively uncommon, with an estimated frequency of up to 10% of ischemic strokes, the findings in this patient are consistent with the so-called malignant MCA syndrome. Younger age, female gender, absence of prior stroke, and the presence of the hyperdense MCA sign and hypodensity involving greater than 50% of the MCA territory on noncontrast head CT have all been associated with neurologic deterioration.

▶ **22.** A 66-year-old woman with a history of hypertension is brought to the emergency department at 8.00 AM because she awoke with acute onset of left-sided weakness in the left side of the body 1 hour before. According to the patient and her husband, she was normal when she went to bed at 9:00 PM the previous night. Evaluation on arrival reveals a left hemiparesis and dysarthria. Blood pressure is 175/100 mm Hg. A CT scan shows early ischemic changes in the right insula and lenticular nucleus. EKG, cardiac enzymes, blood glucose, platelet count, prothrombin time, and activated partial thromboplastin time are normal. Which of the following is the most appropriate treatment for this patient according to current guidelines?

A. Aspirin
B. Heparin

C. Intraarterial recombinant tissue-type plasminogen activator
D. IV recombinant tissue-type plasminogen activator
E. Labetalol

The correct answer is A. Initiation of antiplatelet therapy within 48 hours of ischemic stroke has been shown to be effective at preventing recurrent ischemic stroke. For a patient who awakens with symptoms, the time of onset is considered to be the time when the patient went to bed, assuming that the patient was known to be normal at this time, which is the case with this patient. Thus, this patient is beyond the therapeutic window for either IV or intraarterial recombinant tissue-type plasminogen activator. The role of hyperacute anticoagulation is not yet well defined, although numerous acute stroke trials suggest that the risk of intracerebral hemorrhage outweighs any benefit. Unless there is jeopardy to target organs, aggressive lowering of blood pressure is not indicated in the setting of acute stroke as it may reduce blood flow to the ischemic penumbra and to areas lacking cerebral autoregulation.

▶ **23.** In a recent prospective study of 300 patients with suspected strokes conducted in an urban teaching hospital, about one-third of patients were ultimately diagnosed with stroke mimics. Which of the following factors correlated most strongly with an ultimate accurate diagnosis of stroke?

A. Age over 55
B. Concurrent headache
C. History of focal neurologic symptoms
D. History of prior stroke
E. Normal metabolic profile in the emergency department

The correct answer is C. According to the authors of the chapter "Diagnosis of Stroke and Stroke Mimics in the Emergency Setting" in the prospective study by Hand and colleagues (2006), eight variables were independently associated with a correct diagnosis of stroke. Of those, the two most powerful predictors were a definite history of focal neurologic symptoms (choice C) and an NIH Stroke Scale score greater than 10. The most common stroke mimic in this study was the postictal state, followed by sepsis and toxic-metabolic encephalopathies.

Hand PJ, Kwan J, Lindley RI, et al. Distinguishing between stroke and mimic at the bedside: the brain attack study. Stroke 2006;37(3):769–775.

▶ **24.** A 60-year-old right-handed woman is evaluated for acute onset of left arm and face weakness 2 hours ago. She has a history of hypertension that is well controlled with hydrochlorothiazide. At the time of her evaluation in the emergency department, her left arm weakness had improved slightly. She was found to have a blood pressure reading of 160/100 mm Hg, and she was treated with labetalol, resulting in a reduction of blood pressure to her basal levels of 140/90 mm Hg. A few minutes later, however, her weakness worsened, resulting in left hemiplegia. Which of the following mechanisms is most likely to explain the neurologic deterioration in this patient?

A. Hemorrhagic transformation
B. Ischemic vasoconstriction

C. Loss of autoregulation
D. Neuronal hyperpolarization
E. Vasogenic edema

The correct answer is C. A typical feature of the area of ischemic penumbra is maximum vasodilatation, which disrupts cerebral blood flow autoregulation and makes local blood flow directly dependent on the cerebral perfusion pressure. Transient increase in arterial pressure in the setting of acute stroke may provide a protective mechanism that maintains cerebral perfusion pressure in this region. Lowering of arterial pressure, particularly in patients with chronic hypertension (resulting in leftward shift of the autoregulatory curve) may result in reduced blood flow in this jeopardized area, thus worsening neurologic symptoms either reversibly or irreversibly (by incorporating these neurons into the "core").

▶ **25.** Very early initiation of neuroprotective therapies is one approach being investigated for preservation of the penumbra in early stroke. Which of the following factors places the greatest limitation on the development and evaluation of potential neuroprotective therapies?

A. Many patients will ultimately have stroke mimics
B. Many therapies cannot be given during prehospital transport
C. Many therapies may conflict with common medications
D. Most patients are treated too late to help
E. Neuroprotective agents are not profitable for pharmaceutical companies

The correct answer is D. The authors of the chapter "Emerging Therapies" note that neuroprotection trials may have failed because drug was administered in late time windows when most of the brain infarction had already occurred. Neuroprotection will need to be initiated much earlier if the drugs are safe enough to use in the ambulance to patients even without stroke.

▶ **26.** The recent Joint Commission stroke-specific care performance measures include which of the following treatment requirements?

A. Discharge on a cholesterol-lowering medication
B. Discharge on an angiotensin-converting enzyme inhibitor
C. Screen for dysarthria
D. Start antithrombotic therapy by the end of the first week of hospitalization
E. Start antithrombotic therapy within 2 months of discharge

The correct answer is A. Joint Commission stroke-specific care performance measures include discharge on cholesterol-lowering medication, as well as deep venous thrombosis prophylaxis, anticoagulation therapy for patients with atrial fibrillation, antithrombotic therapy by end of hospital day 2, discharge on antithrombotic therapy, dysphagia screening, stroke education, smoking cessation/advice/counseling, and assessment for rehabilitation.

▶ **27.** A 35-year-old woman is evaluated because she noticed that she became acutely unable to read the newspaper 2 hours ago. On examination she is alert and oriented and has no focal weakness. She is able to write a simple

sentence on dictation but is unable to read it. This is most likely due to an infarction in which of the following vascular territories?

A. Left lenticulostriate
B. Left middle cerebral
C. Left posterior cerebral
D. Right middle cerebral
E. Right posterior cerebral

The correct answer is C. The patient has alexia without agraphia, which typically occurs with lesions in the territory of the left posterior cerebral artery. The classic lesion involves the left calcarine cortex or optic radiations (producing right hemianopsia) plus the splenium of the corpus callosum, interrupting the connections from the right to the left occipital association cortex, which provides access to areas involved in recognition of words.

▶ **28.** Which of the following is the objective of a phase 2 clinical trial on a new drug?

A. To assess bioavailability of the drug in the target tissue
B. To determine how the drug is working in the "real world," both in terms of efficacy and safety, after US Food and Drug Administration (USFDA) approval
C. To determine whether the drug produces toxic effects on experimental animals
D. To obtain comparative information about relative safety and efficacy of the drug in a randomized controlled trial (RCT)
E. To obtain, in an RCT, definite data on the drug's benefits and risks based on promising results from previous RCTs

The correct answer is D. Most phase 2 studies are RCTs, often blinded, to obtain comparative information about the relative safety and efficacy of a new drug. Phase 1 trials typically assess safety and feasibility. Phase 3 RCTs are typically for definitive data on a treatment's risk and benefit based on promising results from phase 2 trials. Phase 4 trials are post-USFDA-approval studies to assess the safety and efficacy of the treatment in the targeted patient population.

▶ **29.** Which of the following interventions is recommended as a first-line treatment for controlling hypertension *after* the administration of recombinant tissue-type plasminogen activator?

A. Bolused, then infused, labetalol
B. Infused IV clonidine
C. Infused IV nimodipine
D. IV sodium nitroprusside drip
E. Nitropaste

The correct answer is A. The authors of the chapter "IV Thrombolytic Therapy for Acute Ischemic Stroke" enumerate several approaches to treating hypertension after recombinant tissue-type plasminogen activator (rt-PA) administration as per 2007 American Heart Association guidelines. As opposed to treating hypertension *prior* to rt-PA, the recommendation postinfusion is

for aggressive blood pressure treatment. Recommended first-line agents are IV labetalol, nitropaste, or infused nicardipine (choice A). Sodium nitroprusside (choice D) is not recommended as a first-line agent.

▶ **30.** In order to develop a successful primary stroke center, the authors of the chapter "Primary Stroke Center Certification" outline numerous resources that should be made available and requirements that should be met. In order to ensure improved patient outcomes, which of the following is continually emphasized by the authors?

A. Admission orders should be tailored to the individual patient
B. Constant documentation and logbooks must be kept
C. Emergency department personnel should defer to neurologists for stroke management
D. A stroke center is best led by a group of physicians
E. The stroke team should respond within 1 hour of being notified

The correct answer is B. The authors of the chapter "Primary Stroke Center Certification" relate in detail current Joint Commission criteria for stroke center certification and outline their interpretation of these guidelines. They state that while a stroke center's staff will inevitably comprise individuals from multiple disciplines, ideally there should be a director who is most likely to be a neurologist. Admission orders should be standardized and not highly variable, and emergency department personnel must be trained to initiate acute stroke care. Answer B is continually emphasized by the authors: in order to critically analyze outcomes and improve care, stringent case-by-case documentation of all facts of care must be undertaken by the stroke center.

▶ **31.** A 70-year-old man is brought to the emergency department 1 hour after the onset of difficulty speaking and right-hand clumsiness. He has a history of coronary artery disease, type 2 diabetes mellitus, hypertension, and hyperlipidemia. He underwent coronary artery bypass grafting 2 years ago and a cystoscopy 3 weeks ago. One year ago, a small thalamic hemorrhage was found after he underwent a head CT done after a confusional episode. On examination, he is alert. Blood pressure is 170/90 mm Hg and heart rate 55 beats per minute. Language is nonfluent with difficulty naming and repeating as well as with writing. Comprehension is generally preserved. Right upper extremity pronator drift and difficulty with fine motor movements in the right hand are present. A noncontrast CT of the brain is normal. The treating physicians are considering the use of recombinant tissue-type plasminogen activator (rt-PA). Which of the following excludes the use of rt-PA in this patient?

A. Elevated blood pressure
B. Inability to give informed consent
C. Prior coronary artery bypass grafting
D. Prior intracranial hemorrhage
E. The recent urologic procedure

The correct answer is D. The authors of the chapter "Intravenous Thrombolytic Therapy for Acute Ischemic Stroke" provide a table of

current eligibility criteria (American Heart Association guidelines) for the use of rt-PA (see **Table 3-3**). The patient's cystoscopy, aside from not being major surgery, was more than 2 weeks ago, and prior coronary artery bypass grafting is not an exclusionary criterion unless the time requirement (2 weeks out) is not met. This patient's blood pressure is within established boundaries for rt-PA administration (greater than 185 mm Hg systolic, greater than 110 mm Hg diastolic). The patient, although aphasic, seems able to comprehend enough to understand the consent form (which could also be given to a family member); furthermore, informed consent would not be necessary for IV rt-PA patients who meet standard eligibility criteria. Although it seems that the patient suffered no residua from his prior thalamic hemorrhage, prior intracranial hemorrhage is an exclusionary criterion.

▶ **32.** A group of researchers begins to recruit patients for an acute stroke trial involving a medication designed to limit the area of infarct in cortical strokes. The medication used has shown promising results in phase 2 trials involving small numbers of patients. After 6 months, the number of patients recruited falls 30% short of the target. Some of the investigators suggest changing the protocol to include subcortical strokes. According to the authors of the chapter "'How To' Guide for Clinicians Interested in Becoming Involved in Clinical Stroke Research," what is a potential drawback of this strategy?

A. The drug may not work for a different pathophysiology
B. The investigators will appear to be motivated by personal gain
C. It may be unethical to change the rules midway through the trial
D. The mechanism of action may not be understood
E. There is potential to harm those recruited under new criteria

The correct answer is A. The authors of the chapter "'How To' Guide for Clinicians Interested in Becoming Involved in Clinical Stroke Research" address the issue of revising a clinical trial protocol while a study is in progress. According to the authors, certain ethical considerations are already a given in a trial (eg, consent obtained from someone other than the treating physician, no financial conflicts of interest with use of a particular experimental agent), and, therefore, no particular ethical consideration is raised in revising protocols. However, they do cite the example of broadening inclusion criteria in stroke trials (in an attempt to recruit more subjects) leading to failure of a trial because of presumed different pathophysiology not targeted by the experimental drug.

▶ **33.** Deep venous thrombosis (DVT) is a well-recognized severe complication of acute ischemic stroke. The authors of the chapter "Complications of Ischemic Stroke: Prevention and Management" discuss the Prevention of Venous Thromboembolism After Acute Ischaemic Stroke (PREVAIL) trial, designed to determine the optimal anticoagulant for use in prevention of poststroke DVT. They note, however, that despite the fact that the PREVAIL trial was well designed, its efficacy and safety end points failed to determine whether enoxaparin (low-molecular-weight heparin) or unfractionated

heparin was a better treatment. Which of the following statements summarizes the results of this trial?

A. Both therapies are effective in preventing DVTs.
B. Enoxaparin is not cost-effective.
C. Enoxaparin produced fewer systemic hemmorhages.
D. Results were indeterminate.
E. Unfractionated heparin is more hazardous in general.

The correct answer is A. The authors note that in the PREVAIL trial, enoxaparin prevented more asymptomatic DVTs but had a higher rate of extracranial hemorrhages. Cost is not raised as an issue. Unfractionated heparin and enoxaparin were basically equivalent and effective in preventing symptomatic DVTs and fatal pulmonary emboli. Unfractionated heparin had a lower rate of hemorrhagic complications.

▶ **34.** A 46-year-old right-handed woman is evaluated for acute onset of left hemiplegia and sensory loss. A CT scan of the head shows loss of gray-white matter differentiation in the right middle cerebral artery territory. Which of the following mechanisms may reduce NMDA-mediated excitotoxic neuronal loss in this area?

A. Activation of matrix metalloproteinases
B. Calcium release from the endoplasmic reticulum
C. Extracellular acidosis
D. Inhibition of glutamate transport by astrocytes
E. Neuronal depolarization

The correct answer is C. Activation of NMDA receptors by L-glutamate, by increasing influx of calcium to neurons and glial cells, is an important trigger of cell death (excitotoxicity) in the setting of cerebral ischemia. Acidosis reduces the probability of opening of the NMDA receptor-linked calcium channel. In contrast, impaired astrocyte glutamate transport (leading to synaptic accumulation of L-glutamate), neuronal depolarization, and release of intracellular calcium all potentiate NMDA receptor–mediated excitotoxicity. Activation of matrix metalloproteinases disrupts the blood-brain barrier, allowing influx of inflammatory cells that release cytokines, which potentiates NMDA receptor–mediated injury.

▶ **35.** A 62-year-old man with a history of hypertension and hypercholesterolemia treated with lisinopril, atorvastatin, hydrochlorothiazide, and aspirin is brought to the emergency department at 60 minutes after acute-onset left-sided weakness. Evaluation upon arrival reveals a left hemiparesis and dysarthria. Blood pressure is 160/90 mm Hg. A CT scan shows early ischemic changes in the right insula. EKG, cardiac enzymes, blood glucose, platelet count, prothrombin time, and activated partial thromboplastin time test results are normal. The patient has no history of head trauma, stroke, hemorrhage, or recent surgeries or arterial punctures. Which of the following is a potential risk of IV recombinant tissue-type plasminogen activator (rt-PA) in this patient?

A. Angioedema
B. Hyponatremia

C. Myonecrosis
D. Rash
E. Seizures

The correct answer is A. Angioedema is typically seen in 1% to 2% of patients treated with IV rt-PA and is more common in patients receiving angiotensin-converting enzyme inhibitors and with insular or frontal strokes.

▶ **36.** According to the authors of the chapter "'How To' Guide for Clinicians Interested in Becoming Involved in Clinical Stroke Research," which of the following criteria should be met before entering patients into clinical trials?

A. The different phases of clinical trials should be explained to patients
B. Expenses related to the trial are the patient's responsibility
C. Free drug should be given if the trial is successful
D. Patients must agree to complete the trial
E. The trial must have a placebo arm

The correct answer is A. According to the authors of the chapter "'How To' Guide for Clinicians Interested in Becoming Involved in Clinical Stroke Research," patients should have an understanding of the meaning of the various phases of clinical trials so that they can better evaluate the potential risks and benefits of entering a trial. Although free drug is sometimes provided in extension periods after the completion of clinical trials, this is not always the case. Study-related expenses should be covered by the study budget. Patients have the right to opt out of a clinical trial at any time. If an effective approved therapy exists, the study will most likely not have a placebo arm.

▶ **37.** A 56-year-old right-handed woman is evaluated for acute onset of left hemiplegia 2 hours ago. A CT scan of the head shows loss of gray-white matter differentiation in the left insular cortex and basal ganglia. There is an area of diffusion-weighted imaging (DWI)/perfusion-weighted imaging (PWI) mismatch on MRI. Which of the following statements best describes the area of ischemic penumbra in this case?

A. The area of penumbra includes neurons that are at risk of undergoing apoptosis.
B. The cerebral blood flow in the area of ischemic penumbra is typically less than 7 mL/100 g/min.
C. The DWI abnormalities correspond to a core that remains unchanged with the duration of ischemia.
D. The DWI abnormalities precisely delineate the area of irreversible cell damage.
E. The DWI abnormality represents areas of increased permeability of the blood-brain barrier.

The correct answer is A. It has been shown that the DWI lesion, which represents areas of intracellular edema, is not precise in distinguishing between reversible and irreversible ischemia. The area of PWI/DWI mismatch includes jeopardized neurons that are at risk of irreversible

damage if perfusion is not restored. The accumulative risk increases with the duration of ischemia, which may lead to progressive increase of the core at the expense of the penumbra.

▶ **38.** A 65-year-old man with a history of hypertension, hyperlipidemia and type 2 diabetes mellitus notes the acute onset of unsteadiness with inability to walk 30 minutes after returning from the golf course. He is mildly nauseated but does not have vertigo. His glucometer reading at home is 130. He is taken by ambulance to an emergency department (ED) where he is examined by an ED resident 90 minutes after the onset of his symptoms. Vital signs show a blood pressure of 170/90 mm HG and are otherwise normal, as is his blood sugar. Further examination shows gaze-evoked nystagmus with mildly slurred speech. Finger-to-nose and heel-to-shin testing are fairly unremarkable. The NIH Stroke Scale (NIHSS) score is 1. He stands with assistance but is completely unable to walk, listing to the left. The radiology department calls to report an abnormal diffusion-weighted imaging reading on MRI. What is the most likely explanation for the inconsistency between the clinical findings and the NIHSS score?

A. Dysarthria is not a component of the scale
B. It was performed by a non-neurologist
C. It was performed too acutely
D. The NIHSS does not provide a comprehensive neurologic assessment
E. The patient probably did not have a stroke

The correct answer is D. The NIHSS, according to the authors, includes a relatively cursory examination of cranial nerve and cerebellar functions and does not assess gait impairment due to causes other than weakness. Even patients with some limb ataxia and dysarthria will emerge with low scores on the scale while their syndromes may be quite disabling (eg, inability to walk). In the absence of significant motor deficits on bedside testing, gait assessment should be performed in all patients.

▶ **39.** In the Interventional Management of Stroke I and II pilot studies, reduced-dose IV recombinant tissue-type plasminogen activator (rt-PA) was combined with intraarterial rt-PA delivered either by microcatheter or an EKOS MicroLysus® Ultrasound Catheter. Approximately what additional percentage of patients achieved distal perfusion when intraarterial methods were combined with IV treatment?

A. No advantage to combined therapy
B. 10%
C. 25%
D. 60%
E. 100%

The correct answer is D. The authors report that in the Interventional Management of Stroke (IMS)-1 study (combining IV reduced-dose rt-PA and intraarterial rt-PA delivered by microcatheter) and the IMS-2 study (microultrasound catheter plus IV rt-PA), whereas 18% of patients achieved recanalization and reperfusion with low-dose rt-PA, another 60% recanalized and reperfused (for a total of 80%) with the additional intraarterial methods.

► **40.** An 80-year-old man is admitted to a hospital stroke unit 2 hours after awakening with right-sided weakness and slurred speech. He is not treated with thrombolytic therapy and is placed on aspirin. He is initially alert and able to communicate, although he has "thick" speech. He walks with assistance. On the second hospital day, staff notes that he is now weaker on the right side and unable to ambulate to the bathroom. He is afebrile and alert with normal laboratory values. Statistically, according to a large study cited by the authors of the chapter "Complications of Ischemic Stroke: Prevention and Management," what is the most likely reason for deterioration in this patient's neurologic status?

A. Hemorrhagic conversion
B. Hydrocephalus
C. Increased intracranial pressure
D. A new, second stroke
E. Progression of the stroke

The correct answer is E. In the study cited, a large series of patients was looked at for deterioration of neurologic function within the first 2 to 3 days after stroke. The authors found that greater than 13% of patients followed showed deterioration in neurologic status directly attributable to their stroke. Within that group, one-third was found to have progression of their original lesion as the most likely etiology of their functional decline. Hemorrhagic conversion or a second stroke was far less common (about 10% each); increased intracranial pressure accounted for over one-quarter of the cases in this study. Hydrocephalus is not discussed but would be assumed to be relatively uncommon in ischemic stroke.

Weimar C, Mieck T, Buchthal J, et al. Neurologic worsening during the acute phase of ischemic stroke. Arch Neurol 2005;62(3):393–397.

QUINTESSENTIALS®

ACUTE ISCHEMIC STROKE

Continuum Lifelong Learning Neurol 2008;14(6):186–187.

Quintessentials is designed to help practicing neurologists identify and make changes to their practices to improve patient care. Composed of two case-based questionnaires and preferred responses, the program is intended to stimulate thought and help you assess your practice behavior against expert opinion. The comments, references, and links to information provided in this issue of CONTINUUM should assist you in this process.

This program consists of three parts:

Part 1—Baseline

1. Go to *www.aan.com/go/elibrary/continuum/quintessentials* to complete Part 1—Baseline Questionnaire. Alternatively, you may cut out and complete Part 1—Baseline Questionnaire on the following pages and then mail or fax your completed forms to the AAN.
2. Review the preferred responses to the Baseline Questionnaire either online or in this Quintessentials section. The preferred responses direct you to pertinent discussion in the CONTINUUM issue and should help stimulate possible changes in your practice of patients with acute ischemic stroke.

Part 2—Follow-up

Approximately 1 month after receipt of your Part 1—Baseline Questionnaire, the AAN will send you an email reminding you to complete Part 2—Follow-up Questionnaire. If you completed Part 1 on paper, you will need to complete Part 2 on paper, and the AAN will mail the questionnaire to you. This case-based questionnaire will reexamine your knowledge and behaviors related to your practice of patients with acute ischemic stroke.

1. Complete Part 2—Follow-up Questionnaire at *www.aan.com/go/elibrary/continuum/quintessentials*, or mail or fax your completed forms to the AAN.
2. Review the preferred responses to the Follow-up Questionnaire. Like the preferred responses to the Baseline Questionnaire, they will direct you to pertinent discussion in the CONTINUUM issue and should help stimulate possible changes in your practice.

Part 3—Feedback and Evaluation

Upon receipt of your Part 2—Follow-up Questionnaire, you will immediately receive an electronic comparison report of your responses to Part 1—Baseline Questionnaire and Part 2—Follow-up Questionnaire and a program evaluation form. These forms will be sent by mail to participants who have submitted Parts 1 and 2 on paper. The comparison report is intended to help you identify any changes you made in your practice as a result of the program.

1. Complete the evaluation form at *www.aan.com/go/elibrary/continuum/quintessentials* or mail or fax the evaluation form to the AAN in order to be granted CME for participation in the program.

2. A transcript of credits earned in Quintessentials Acute Ischemic Stroke will be available to you electronically in two business days. If you completed the module on paper, you will be sent your transcript within 2 months of receipt of your evaluation form.

Faculty

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Relationship Disclosure: *Dr Barrett has nothing to disclose.*
Unlabeled Use of Products/Investigational Use Disclosure: *Dr Barrett has nothing to disclose.*

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Learning Objectives

▶ Upon completion of Quintessentials Acute Ischemic Stroke, the participant will be able to:
- Expeditiously evaluate a patient with suspected acute stroke
- Utilize clinical and radiographic criteria to determine eligibility for treatment with IV recombinant tissue-type plasminogen activator (rt-PA)
- Properly care for the patient who has received thrombolytic therapy
- Recognize and manage potential complications after treatment with rt-PA

CORE COMPETENCIES

Quintessentials Acute Ischemic Stroke covers the following core competencies: Patient Care, Medical Knowledge, and Systems-Based Practice.

ESTIMATED TIME TO COMPLETE

The estimated time to complete Parts 1 and 2 is 3 hours.

ACCREDITATION

The American Academy of Neurology (AAN) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The AAN designates this educational activity (Quintessentials Acute Ischemic Stroke) for a maximum of 3 hours of AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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AMERICAN ACADEMY OF NEUROLOGY

ACUTE ISCHEMIC STROKE

Part 1—Baseline Questionnaire

Continuum subscribers may complete and submit this questionnaire online at *www.aan.com/go/elibrary/continuum/quintessentials.*

First Name _____ MI ____ Last Name _____ AAN ID #* _____ Today's Date: ____/____/____ (mm/dd/yyyy)

*If you do not know your AAN ID# or do not have an AAN ID#, contact AAN Member Services at *memberservices@aan.com* or (800) 879-1960, (651) 695-1940 international.

Mailing Address (Number and Street Address) _____

City _____ State _____ Zip Code _____ Country _____ Phone Number _____

Part 2 will be sent to you in 4 weeks. Participation in the Quintessentials Acute Ischemic Stroke module closes on December 31, 2011. For questions regarding CME, please call (651) 695-2706.

- This questionnaire is designed to allow you to benchmark your knowledge of the practice of acute ischemic stroke.
- You will be able to use this self-audit information, in conjunction with other information provided to you through this module, to identify areas in which you may want to improve your practice.
- You will be identified with your responses only in your personalized reports.
- Answer the following questions as you would actually perform these activities.

Directions: Please complete each question as thoroughly as possible. Your responses will be kept confidential.

Case 1

History: A 72-year-old man is gardening with his wife when he develops trouble speaking. She asks him a question several times, but he does not respond. He appears unsteady on his feet and drops his spade from his right hand. His wife is able to help him to the ground, and she notes that he is unable to move his right side. He does not lose consciousness but appears "dazed," and his wife is unable to communicate with him despite repeated efforts. After several minutes, she calls 911. The patient arrives in the local emergency department 45 minutes after symptom onset.

Past Medical History: Hypertension, hyperlipidemia, osteoarthritis.

Past Surgical History: Appendectomy, lumbar laminectomy.

Medications: Amlodipine 10 mg daily, atorvastatin 20 mg daily, aspirin 81 mg daily, chondroitin sulfate 1200 mg daily.

Family History: No family history of stroke or neurologic disease. Mother and brother with hypertension.

Social History: Retired civil engineer. Married for 51 years. Remote tobacco use; quit more than 30 years ago. No regular alcohol use.

During the initial clinical assessment of this patient, how likely are you to perform the following?

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
1. A full neurologic examination (ie, detailed evaluation of mental status, sensation, etc)	❍	❍	❍	❍
2. A focused neurologic examination using a standardized assessment tool	❍	❍	❍	❍

Examination: Temperature 37.1°C, blood pressure 179/89 mm Hg, pulse 91 and irregular, respirations 16. He is awake, alert, and in no distress. The neck is supple. No cervical bruits or cardiac murmurs are present. He is unable to state his age or the current month. He is able to close his eyes to command but protrudes his tongue when asked to make a fist with his left hand. He is unable to read or name objects. There is a left gaze preference that can be overcome with vigorous stimulation from the right side. No appreciable visual field deficit is present. The motor examination demonstrates dense hemiparesis involving the right lower face, arm, and leg. There are trace distal movements in the right hand and foot. The sensory examination is remarkable for decreased pin sensation in the right face, arm, and leg. There is no evidence of ataxia or hemispatial neglect.

How likely are you to order the following tests in the evaluation of this patient?

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
3. Finger-stick glucose	❍	❍	❍	❍
4. Complete blood count	❍	❍	❍	❍
5. Lumbar puncture	❍	❍	❍	❍
6. Coagulation profile (activated partial thromboplastin time [aPTT], international normalized ratio)	❍	❍	❍	❍
7. Chest radiograph	❍	❍	❍	❍
8. Noncontrast head CT	❍	❍	❍	❍

After obtaining normal laboratory and noncontrast head CT results, how likely are you to administer the following medications to this patient 100 minutes after symptom onset?

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
9. IV unfractionated heparin infusion to achieve aPTT 2.5 times the baseline value	❍	❍	❍	❍
10. IV recombinant tissue-type plasminogen activator (rt-PA)	❍	❍	❍	❍

How likely are you to administer IV rt-PA to an otherwise eligible patient with the following findings on noncontrast head CT?

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
11. Intraparenchymal hyperintensity in a clinically relevant area	❍	❍	❍	❍
12. Loss of gray-white differentiation in the insular cortex or lentiform nucleus	❍	❍	❍	❍
13. Well-demarcated area of hypodensity with mass effect involving greater than one-third of the middle cerebral artery territory in the clinically relevant hemisphere	❍	❍	❍	❍

Prior to administration of IV rt-PA to an eligible patient with stroke, how likely are you to obtain the following?

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
14. Testing for stool guaiac	❍	❍	❍	❍
15. Written informed consent	❍	❍	❍	❍

Case 2

History: A 53-year-old man arrives in the emergency department by ambulance 1 hour after he suddenly developed slurred speech and difficulty walking. His son was with him when the symptoms began, and he reports that his father was "staggering" and appeared "sweaty." The patient reports no headache, visual changes, or loss of feeling. There was no witnessed loss of consciousness and no prior history of stroke or TIA.

Past Medical History: Coronary artery disease, peripheral vascular disease, hypertension, non–insulin-dependent diabetes, hyperlipidemia.

Past Surgical History: Percutaneous coronary angioplasty and two stents.

Medications: Aspirin 325 mg daily, clopidogrel 75 mg daily, amlodipine 10 mg daily, hydrochlorothiazide 25 mg daily, lisinopril 10 mg daily, simvastatin 20 mg daily.

Family History: Mother with diabetes. Father deceased with stroke. Two "healthy" brothers.

Social History: Smokes 1.5 packs of cigarettes daily. Drinks two to three beers nightly.

Examination: Temperature 37.6°C, blood pressure 200/99 mm Hg, pulse 95 and regular, respirations 18. The general physical examination is remarkable for a left cervical bruit and a 2/6 systolic ejection murmur heard best at the right upper sternal border with radiation to the suprasternal notch. He is able to correctly state his age and the current month. There is no evidence of aphasia or neglect. There is no gaze preference or visual field deficit. Ocular motility is full with persistent nystagmus on left lateral gaze. Speech is markedly dysarthric. The motor examination is normal without evidence of drift. The sensory examination shows no evidence of sensory asymmetry to pin or hemispatial neglect. There is marked ataxia on finger-to-nose testing of the left arm and heel-to-shin testing of the left leg.

Management: The patient undergoes a noncontrast head CT that shows no evidence of acute intracranial hemorrhage. The finger-stick glucose level is 121. The remainder of the laboratory evaluation is within normal limits. There is no past history of intracranial hemorrhage, recent head trauma, recent surgical procedures, gastrointestinal or genitourinary hemorrhage, or recent arterial puncture. A bolus of IV labetalol 20 mg is administered, and the blood pressure 5 minutes later is 176/78 mm Hg. The risks, benefits, and alternatives of IV rt-PA are discussed with the patient and his family. Alteplase 0.9 mg/kg is ordered; 10% of the dose is given as a bolus over 1 minute, and the remainder of the dose is started as a continuous infusion over the next hour.

How likely are you to recommend continued care for this patient in the following setting?

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
16. A monitored bed on a general medical ward	❍	❍	❍	❍
17. A medical or neurologic intensive care unit	❍	❍	❍	❍

Following transfer to an appropriate unit, how likely are you to recommend the following for this patient?

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
18. Intraarterial blood pressure monitoring	❍	❍	❍	❍
19. Unfractionated heparin 5000 international units 3 times daily	❍	❍	❍	❍
20. Lower extremity sequential pneumatic compression devices	❍	❍	❍	❍

Investigations: Thirty minutes after initiation of rt-PA therapy a blood pressure of 235/110 mm Hg is obtained.

How likely are you to administer the following agents to this patient?

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
21. Sodium nitroprusside	❍	❍	❍	❍
22. IV nicardipine infusion at 5 mg/h	❍	❍	❍	❍

Interval Case History: Shortly after the elevated blood pressure measurement, a change occurs in the patient's neurologic condition. The patient reports a severe occipital headache, and his speech is more dysarthric. He vomits once, and the headache continues to worsen.

In response to the change in the patient's clinical condition, how likely would you be to perform the following?

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
23. Administer oxycodone + acetaminophen 5/100 two tablets by mouth	❍	❍	❍	❍
24. Discontinue rt-PA infusion	❍	❍	❍	❍
25. Order an urgent noncontrast head CT	❍	❍	❍	❍

Investigations Continued: The noncontrast head CT reveals a cerebellar hemorrhage.

How likely are you to perform the following?

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
26. Administer antithrombin III	❍	❍	❍	❍
27. Administer cryoprecipitate and platelets	❍	❍	❍	❍
28. Obtain neurosurgical consultation	❍	❍	❍	❍

Thank you for your time.

Please send your completed survey by fax to **(651) 361-4806** or by mail to:

Lori Strachota
American Academy of Neurology
1080 Montreal Avenue
St. Paul MN 55116

Please review the preferred answers, which follow this questionnaire.
Part 2 will be sent to you in 4 weeks.

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ACUTE ISCHEMIC STROKE

Preferred Responses
Part 1—Baseline

The following are the preferred responses accompanied by comments and pertinent links to material presented within this issue of CONTINUUM for the Quintessentials Acute Ischemic Stroke Part 1—Baseline Questionnaire. The cases and questions are repeated, and the preferred responses are indicated in bold. On the CONTINUUM pages referenced in this section you will see yellow-shaded text including material specific to the question. No score will be assigned to the questionnaire you complete since the emphasis of this program is on self-assessment. You are encouraged to review the responses and explanations carefully and consider making changes in your practice. One month after you submit the Part 1—Baseline Questionnaire online, you will receive an email reminder to complete Part 2—Follow-up Questionnaire, which will help you assess whether you have adjusted your practice behavior based on the learning points provided in the Part 1 preferred responses. If you submitted the questionnaire by mail or fax, you will receive Part 2 by mail.

Case 1 (Acute Ischemic Stroke—Eligible for IV Recombinant Tissue-Type Plasminogen Activator)

History: A 72-year-old man is gardening with his wife when he develops trouble speaking. She asks him a question several times, but he does not respond. He appears unsteady on his feet and drops his spade from his right hand. His wife is able to help him to the ground, and she notes that he is unable to move his right side. He does not lose consciousness but appears "dazed," and his wife is unable to communicate with him despite repeated efforts. After several minutes, she calls 911, and the patient arrives in the local emergency department 45 minutes after symptom onset.

Past Medical History: Hypertension, hyperlipidemia, osteoarthritis.

Past Surgical History: Appendectomy, lumbar laminectomy.

Medications: Amlodipine 10 mg daily, atorvastatin 20 mg daily, aspirin 81 mg daily, chondroitin sulfate 1200 mg daily.

Family History: No family history of stroke or neurologic disease. Mother and brother with hypertension.

Social History: Retired civil engineer. Married for 51 years. Remote tobacco use; quit more than 30 years ago. No regular alcohol use.

During the initial clinical assessment of this patient, how likely are you to perform the following?

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
1. A full neurologic examination (ie, detailed evaluation of mental status, sensation, etc)	❍	●	❍	❍

The time-sensitive nature of acute stroke therapy necessitates an expeditious examination focused on identifying signs of lateralized hemispheric or brainstem dysfunction suggestive of focal cerebral ischemia **(page 15)**. Many elements of the full neurologic examination require a degree of patient cooperation and attention that may be difficult to achieve in a high-acuity setting (ie, emergency department).

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
2. A focused neurologic examination using a standardized assessment tool	❍	❍	❍	●

The NIH Stroke Scale (NIHSS) is a standardized clinical assessment tool that measures key aspects of neurologic function often involved in stroke syndromes. The NIHSS can be performed rapidly, and providers can be trained to reliably perform the assessment in a short period of time. The NIHSS allows quantitative measurement of stroke severity, facilitates communication between providers regarding a patient's neurologic status, and can capture changes in neurologic status over time (**page 16**).

Examination: Temperature 37.1°C, blood pressure 179/89 mm Hg, pulse 91 and irregular, respirations 16. He is awake, alert, and in no distress. The neck is supple. No cervical bruits or cardiac murmurs are present. He is unable to state his age or the current month. He is able to close his eyes to command but protrudes his tongue when asked to make a fist with his left hand. He is unable to read or name objects. There is a left gaze preference that can be overcome with vigorous stimulation from the right side. No appreciable visual field deficit is present. The motor examination demonstrates dense hemiparesis involving the right lower face, arm, and leg. There are trace distal movements in the right hand and foot. The sensory examination is remarkable for decreased pin sensation in the right face, arm, and leg. There is no evidence of ataxia or hemispatial neglect.

How likely are you to order the following tests in the evaluation of this patient?

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
3. Finger-stick glucose	❍	❍	❍	●

Guidelines recommend routine testing of blood glucose in patients with suspected stroke (**page 50; Table 3-2**). Hypoglycemia and hyperglycemia may present with strokelike symptoms, and these conditions can be readily identified by measurement of finger-stick blood glucose. A blood glucose concentration of greater than 50 mg/dL (2.7 mmol/L) is necessary for IV recombinant tissue-type plasminogen activator (rt-PA) eligibility (**page 51; Table 3-3**).

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
4. Complete blood count	❍	❍	❍	●

Guidelines recommend routine testing of the complete blood count in patients with suspected stroke (**page 50; Table 3-2**). Thrombocytopenia may increase the risk of hemorrhagic complications with reperfusion therapy, and eligibility criteria for IV rt-PA include a platelet count of greater than 100,000 mm^3 (**page 51; Table 3-3**).

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
5. Lumbar puncture	●	❍	❍	❍

The routine evaluation of a patient with stroke does not include lumbar puncture unless symptoms suggestive of subarachnoid hemorrhage are present (**page 14**). Subarachnoid hemorrhage should be considered in a patient with a severe headache that reaches maximal intensity at onset or within seconds of onset. If such a history is elicited, lumbar puncture may be warranted to exclude a small subarachnoid bleed from an unruptured intracranial aneurysm (ie, sentinel leaks) when blood is not evident on routine noncontrast head CT.

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
6. Coagulation profile (activated partial thromboplastin time [aPTT], international normalized ratio)	❍	❍	❍	●

Routine laboratory testing of the aPTT and international normalized ratio (INR) are recommended in patients with suspected stroke (**page 50; Table 3-2**). Eligibility criteria for IV rt-PA include aPTT in the normal range and an INR less than or equal to 1.7 (**page 51; Table 3-3**).

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
7. Chest radiograph	❍	●	❍	❍

The utility of routine chest radiography as part of the acute stroke evaluation is limited (**page 17**). Performing a chest radiograph without a specific indication is likely to introduce unnecessary delays into the evaluation and treatment of eligible patients with stroke.

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
8. Noncontrast head CT	❍	❍	●	❍

Brain imaging is the only reliable means to differentiate between ischemic and hemorrhagic stroke prior to administration of thrombolytic therapy (**pages 17-18**). Noncontrast head CT is sensitive to intracranial blood, is widely available, and can be performed rapidly as part of the acute stroke evaluation. For these reasons, CT remains the most widely used imaging modality in the acute setting. MRI is sensitive to acute cerebral ischemia and intracranial hemorrhage and is an acceptable modality to evaluate patients with acute stroke when readily available.

After obtaining normal laboratory and noncontrast head CT results, how likely are you to administer the following medications to this patient 100 minutes after symptom onset?

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
9. IV unfractionated heparin infusion to achieve aPTT 2.5 times the baseline value	●	❍	❍	❍

Current evidence does not support the use of urgent anticoagulation to prevent early recurrent stroke or neurologic worsening or to improve outcomes after stroke (**page 57**).

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
10. IV recombinant tissue-type plasminogen activator	❍	❍	❍	●

IV rt-PA is the standard of care for patients with acute ischemic stroke within 3 hours of symptom onset (**page 47**). Patients with a clinical syndrome consistent with acute stroke and no laboratory or radiographic contraindications should receive treatment after discussing the risks and benefits with the patient and family. A negative CT scan in the acute setting should not cast doubt on a clinical diagnosis of stroke in the appropriate clinical setting.

How likely are you to administer IV rt-PA to an otherwise eligible patient with the following findings on noncontrast head CT?

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
11. Intraparenchymal hyperintensity in a clinically relevant area	●	○	○	○

An intraparenchymal hyperintensity on noncontrast head CT is indicative of acute hemorrhage and is a contraindication to administration of thrombolytic therapy (**page 18)**.

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
12. Loss of gray-white differentiation in the insular cortex or lentiform nucleus	○	○	○	●

Loss of differentiation of the gray-white matter interface in the insula or lentiform nucleus and sulcal effacement due to focal tissue edema are early CT indicators of ischemia (**page 18**). These so-called early ischemic changes are often identified with the assistance of a radiologist and can be helpful in confirming an early diagnosis of ischemic stroke (**page 18**). In the pivotal clinical trial demonstrating the efficacy of rt-PA, the presence of early ischemic changes was not independently associated with adverse outcome after rt-PA treatment. Therefore, early ischemic changes should not directly influence therapeutic decisions.

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
13. Well-demarcated area of hypodensity with associated mass effect involving greater than one-third of the middle cerebral artery territory in the clinically relevant hemisphere	●	○	○	○

In contrast to subtle early ischemic changes, a clearly delineated area of hypodensity with associated mass effect is a contraindication to IV rt-PA (**page 51; Table 3-3**). A distinct hypodensity in a clinically relevant brain region is unlikely to develop within 3 hours of stroke onset and should prompt reconsideration of the time of symptom onset.

Prior to administration of IV rt-PA to an eligible patient with stroke, how likely are you to obtain the following?

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
14. Testing for stool guaiac	○	●	○	○

Testing for stool guaiac is not routinely recommended unless a specific indication such as melena or hematochezia exists (**page 17**).

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
15. Written informed consent	○	●	○	○

IV rt-PA is the standard of care for acute ischemic stroke, and written consent is not required prior to treatment (**page 53**). However, a full discussion of the potential risks, benefits, and alternatives should be discussed with the patient and/or family when possible.

Case 2 (Acute Ischemic Stroke—Postthrombolysis)

History: A 53-year-old man arrives in the emergency department by ambulance 1 hour after he suddenly developed slurred speech and difficulty walking. His son was with him when the symptoms began, and he reports that his father was "staggering" and appeared "sweaty." The patient reports no headache, visual changes, or loss of feeling. There was no witnessed loss of consciousness and no prior history of stroke or TIA.

Past Medical History: Coronary artery disease, peripheral vascular disease, hypertension, non–insulin-dependent diabetes, hyperlipidemia.

Past Surgical History: Percutaneous coronary angioplasty and two stents.

Medications: Aspirin 325 mg daily, clopidogrel 75 mg daily, amlodipine 10 mg daily, hydrochlorothiazide 25 mg daily, lisinopril 10 mg daily, simvastatin 20 mg daily.

Family History: Mother with diabetes. Father deceased with stroke. Two "healthy" brothers.

Social History: Smokes 1.5 packs of cigarettes daily. Drinks two to three beers nightly.

Examination: Temperature 37.6°C, blood pressure 200/99 mm Hg, pulse 95 and regular, respirations 18. The general physical examination is remarkable for a left cervical bruit and a 2/6 systolic ejection murmur heard best at the right upper sternal border with radiation to the suprasternal notch. He is able to correctly state his age and the current month. There is no evidence of aphasia or neglect. There is no gaze preference or visual field deficit. Ocular motility is full with persistent nystagmus on left lateral gaze. Speech is markedly dysarthric. The motor examination is normal without evidence of drift. The sensory examination shows no evidence of sensory asymmetry to pin or hemispatial neglect. There is marked ataxia on finger-to-nose testing of the left arm and heel-to-shin testing of the left leg.

Management: The patient undergoes a noncontrast head CT that shows no evidence of acute intracranial hemorrhage. The finger-stick glucose level is 121. The remainder of the laboratory evaluation is within normal limits. There is no past history of intracranial hemorrhage, recent head trauma, recent surgical procedures, gastrointestinal or genitourinary hemorrhage, or recent arterial puncture. A bolus of IV labetalol 20 mg is administered, and the blood pressure 5 minutes later is 176/78 mm Hg. The risks, benefits, and alternatives of IV rt-PA are discussed with the patient and his family. Alteplase 0.9 mg/kg is ordered; 10% of the dose is given as a bolus over 1 minute, and the remainder of the dose is started as a continuous infusion over the next hour.

How likely are you to recommend continued care for this patient in the following setting?

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
16. A monitored bed on a general medical ward	❍	●	❍	❍

The available resources on a general medical ward are not typically able to provide the required frequent monitoring of vital signs and clinical status during and after rt-PA infusion (**page 53**). Additionally, a general medical ward may not able to provide the resources and monitoring necessary for administration of IV blood pressure medications when clinically indicated.

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
17. A medical or neurologic intensive care unit	❍	❍	❍	●

Observation of a patient in an intensive care unit setting for the first 24 hours after rt-PA administration is generally accepted. The intensive care unit setting provides the support necessary to follow the recommended regimen of clinical and vital sign monitoring every 15 minutes during the rt-PA infusion, every 30 minutes for the next 7 hours, and every hour for the following 16 hours (**page 53**).

Following transfer to an appropriate unit, how likely are you to recommend the following for this patient?

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
18. Intraarterial blood pressure monitoring	●	○	○	○

Placement of intraarterial pressure catheters, indwelling bladder catheters, and nasogastric tubes should be delayed at the time of treatment with IV rt-PA (Adams et al, 2007). The purpose of this recommendation is to reduce the risk of hemorrhage associated with invasive procedures in the immediate period surrounding rt-PA administration. Although frequent monitoring of blood pressure is necessary during and after rt-PA administration, noninvasive cuff measurements should be sufficient in most clinical situations.

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
19. Unfractionated heparin 5000 international units 3 times daily	●	○	○	○

Although the use of low-intensity anticoagulation for deep venous thrombosis prophylaxis is recommended for all immobilized patients with stroke (**page 63**), anticoagulants should not be used during the initial 24-hour period after administration of thrombolytic therapy.

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
20. Lower extremity sequential pneumatic compression devices	○	○	○	●

Although insufficient evidence exists to support the routine use of mechanical compressive devices as the sole method for deep venous thrombosis prophylaxis in acute stroke (**pages 62-63**), the use of these devices is appropriate in the initial 24-hour period postthrombolysis when anticoagulants are contraindicated.

Investigations: Thirty minutes after initiation of rt-PA therapy a blood pressure of 235/110 mm Hg is obtained.

How likely are you to administer the following agents to this patient?

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
21. Sodium nitroprusside	○	●	○	○

Blood pressure greater than 180/105 mm Hg may be a significant risk factor for symptomatic intracranial hemorrhage after rt-PA treatment and warrants aggressive treatment (**page 53**). However, sodium nitroprusside is not considered a first-line agent in the management of hypertension during and after rt-PA treatment (**page 52; Table 3-4**). Sodium nitroprusside lacks a smooth dose response and may cause precipitous declines in blood pressure and excess hypotension, particularly in older adults. Additionally, sodium nitroprusside is a potent arterial and venodilator that may cause an undesired increase in intracranial pressure.

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
22. IV nicardipine infusion at 5 mg/h	○	○	●	○

Nicardipine is recommended as a first-line agent in the management of hypertension during and after rt-PA treatment (**page 52; Table 3-4**). Nicardipine is an arterial vasodilator with a predictable dose-response

relationship and is less likely to cause precipitous changes in blood pressure. The recommended initial infusion rate is 5 mg/h and can be titrated to the desired effect by increasing by 2.5 mg/h every 5 minutes up to a maximum of 15 mg/h. The goal of therapy should be to keep the blood pressure under the acceptable upper limits rather than achieving normotension.

Interval Case History: Shortly after the elevated blood pressure measurement, there is a change in the patient's neurologic condition. The patient reports a severe occipital headache, and his speech is more dysarthric. He vomits once, and the headache continues to worsen.

In response to the change in the patient's clinical condition, how likely would you be to perform the following?

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
23. Administer oxycodone + acetaminophen 5/100 two tablets by mouth	●	❍	❍	❍

The focus of management during and after rt-PA treatment is prevention and detection of symptomatic intracranial hemorrhage **(page 53)**. Clinical signs that may herald intracranial hemorrhage include a sudden increase in blood pressure, worsening or new neurologic deficit, headache, or nausea and vomiting. If these symptoms develop, urgent neuroimaging is warranted and symptomatic treatment can be initiated after exclusion of intracranial hemorrhage.

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
24. Discontinue rt-PA infusion	❍	❍	❍	●

Prompt discontinuation of rt-PA is recommended given the concern for intracranial hemorrhage (**page 53**).

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
25. Order an urgent noncontrast head CT	❍	❍	❍	●

An urgent noncontrast head CT is necessary to exclude symptomatic intracranial hemorrhage (**page 53**).

Investigations Continued: The noncontrast head CT reveals a cerebellar hemorrhage.

How likely are you to perform the following?

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
26. Administer antithrombin III	●	❍	❍	❍

Antithrombin III is not indicated for the management of symptomatic intracranial hemorrhage associated with rt-PA use. Antithrombin III is used for reversal of coagulopathy associated with IV heparin.

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
27. Administer cryoprecipitate and platelets	❍	❍	❍	●

Although no evidence exists to support the optimal approach to management of rt-PA-associated intracranial hemorrhage, current treatment recommendations include urgent transfusion of cryoprecipitate (6 units to 8 units) and platelets (6 units to 8 units) (**page 54; Figure 3-2**). In addition, consultation with a hematologist, if available, is appropriate.

	Definitely Would Not	Probably Would Not	Probably Would	Definitely Would
28. Obtain neurosurgical consultation	❍	❍	❍	●

Neurosurgical consultation is appropriate to discuss the potential risks and benefits of surgical hematoma evacuation, particularly in cases where there is significant mass effect or midline shift (**Figure 3-2**).

REFERENCE

Adams H Jr, del Zoppo G, Alberts M, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists [published errata appears in Stroke 2007;38(6):e38 and Stroke 2007;38(9):e96]. Stroke 2007;38(5):1655–1711.

INDEX

Page numbers in **boldface** type indicate major discussions. Letters after page numbers refer to the following: c = case study; f = figure; r = reference; t = table.

D

E

F

G

H

I

J

L

M

N

O

P

Q

R

S

T

U

V

W

X

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LIST OF ABBREVIATIONS

AAN	American Academy of Neurology
AHA	American Heart Association
APTT	Activated partial thromboplastin time
ASPECTS	Alberta Stroke Programme Early CT Score
CBF	Cerebral blood flow
CBV	Cerebral blood volume
CI	Confidence interval
CME	Continuing medical education
CSC	Comprehensive stroke center
CSF	Cerebrospinal fluid
CT	Computed tomography
CTP	CT perfusion
DNA	Deoxyribonucleic acid
DRG	Diagnosis-related group
DVT	Deep venous thrombosis
DWI	Diffusion-weighted imaging
ED	Emergency department
EEG	Electroencephalogram
EIC	Early ischemic changes
EKG	Electrocardiogram
E/M	Evaluation and management
EMS	Emergency medical services
FLAIR	Fluid-attenuated inversion recovery
GI	Gastrointestinal
GP	Glycoprotein
GRE	Gradient-recalled echo
HIPAA	Health Insurance Portability and Accountability Act
ICU	Intensive care unit
IMS	Interventional Management of Stroke
INR	International normalized ratio
IRB	Institutional review board
IV	Intravenous
LIS	Locked-in syndrome
MAP	Mean arterial pressure
MCA	Middle cerebral artery
MR	Magnetic resonance
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NIH	National Institute of Health
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
NMDA	*N*-methyl-D-aspartate
OR	Odds ratio
PE	Pulmonary embolism
PET	Positron emission tomography
PREVAIL	Prevention of Venous Thromboembolism After Acute Ischaemic Stroke
PROACT II	Prolyse in Acute Cerebral Thromboembolism II
PSC	Primary stroke center
PT	Prothrombin time
PWI	Perfusion-weighted imaging
RCT	Randomized clinical trial
rt-PA	Recombinant tissue-type plasminogen activator
sICH	Symptomatic intracranial hemorrhage
SPECT	Single-photon emission computed tomography
T	Tesla
TCD	Transcranial Doppler
TIA	Transient ischemic attack
TNK	Tenecteplase
t-PA	Tissue plasminogen activator
UFH	Unfractionated heparin
USFDA	US Food and Drug Administration