# Chapter 2
# Ischemic Stroke and Transient Ischemic Attack – Acute Evaluation and Management

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Stroke is the third leading cause of death in the United States behind heart disease and all forms of cancer. Each year 750,000 Americans will have a new or recurrent stroke. Stroke is also the most common medical cause of disability. It is the most highly incident and prevalent neurological condition managed in the hospital setting.

## Pathophysiology of Ischemic Stroke

Ischemic stroke is most often due to a lack of blood flow to all or part of the brain, resulting in the deprivation of neurons of vital glucose and oxygen. This deprivation, if severe and prolonged, results in the interruption of normal cellular processes and eventual cell death with breakdown of the neuronal cell membrane. Ischemia can also result from oxygen deprivation alone (hypoxic–ischemic damage, as may occur in patients who experience a cardiac arrest, respiratory collapse, or both) or glucose deprivation alone (as may occur with insulin overdoses in diabetic patients). A very low (or no) blood pressure can produce a distinct pattern of 'watershed' infarcts, which are typically regions of infarcted tissue between the major cerebral arterial territories. More commonly, ischemic stroke involves only a portion of the brain due to an occlusion of a large or small artery. It also may develop rapidly in multiple arterial territories in the event of multiple emboli or a single embolus which breaks up as it travels.

When an artery is occluded and the brain is deprived of blood flow, there is an almost immediate inhibition of the natural function of the neurons feed by that artery. The neurons cease to perform their normal function, and patients will experience symptoms relevant to the area of the brain involved (weakness, numbness, vision loss, etc.). There is a gradient of blood flow around the location of a large arterial occlusion. So, for example, at the center of the region of ischemia, blood flow may be less than 10 mL/100 g/min. This represents the

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D. Alway, J.W. Cole (eds.), *Stroke Essentials for Primary Care*,
Current Clinical Practice, DOI 10.1007/978-1-59745-433-9_2,

ischemic 'core' of the infarcted region – and these neurons may undergo irreversible cell death in as little as 2 h, if blood flow is not reinstated [1]. As one moves away from this ischemic core, blood flow tends to improve, but is still not considered adequate to maintain survival. This region represents the ischemic penumbra. It is a region surrounding the ischemic core and is considered 'at risk' brain territory. While the existence of an ischemic penumbra in every stroke patient may be in debate, the concept holds that very early intervention (recanalization of the relevant artery within 1 h) is likely to result in no stroke at all while later recanalization (after 2 h) may result in a smaller infarct than otherwise would have occurred.

Transient ischemic attacks (TIAs) involve the same pathophysiology as ischemic strokes, but with an early (usually within 10 min) restoration of blood flow to the brain, and thus, no actual infarction. TIAs were previously defined as stroke symptoms that subsided within 24 h, however, MRI studies with diffusion-weighted imaging revealed that over half of patients whose symptoms lasted greater than 60 min actually had areas of infarction despite resolution of symptoms.

Even if the amount of infarcted tissue does not increase over time, infarcted tissue changes during the coarse of hospitalization, leading to edema or possibly to hemorrhage. Edema of the region of infarction can peak as early as 24 h or as late as 4 days after ischemic onset [2]. Over time, an initially large area of infarction can increase in size leading to increased intracranial pressure, or local pressure effects that can cause obstructive hydrocephalus, further infarction due to pressure on adjacent arteries, or herniation of brain into other compartments. Young patients with large infarctions are the most likely to develop problems related to edema formation.

Areas of infarction may also undergo hemorrhagic transformation, meaning that hemorrhage occurs in the infarcted region. This typically is less problematic than edema formation and may simply be 'petechial' hemorrhages, which are of no clinical significance. Frank hemorrhage with associated clinical deterioration and mass effect occurs in as many as 10% of ischemic stroke patients – typically within the first 2 weeks of the ischemic event. Bleeding disorders (including anticoagulation use), poor blood pressure control, and large infarctions are more prone to such hemorrhages.

## Early Stroke Recognition and Identification of Stroke Type

For many years the management of ischemic stroke largely involved supportive care and physical therapy. Management of risk factors for prevention of secondary stroke was and remains an important aspect of stroke management. With the advent of tissue plasminogen activator (rt-PA) for the acute treatment of ischemic stroke in 1996, the management of stroke changed dramatically. The move toward treatment algorithms founded on evidence-based medicine has also altered the care of the stroke patient. Several states have adopted

legislative Stroke Acts which require emergency medical personnel to transport stroke victims to the nearest certified stroke center. The Joint Commission has developed certification criteria for Primary Stroke Centers based on the published medical literature.

## *Stroke Recognition by the Community*

In order to improve stroke treatment, the community must be educated regarding the symptoms of stroke and the importance of early evaluation and treatment. Too often, patients develop symptoms and signs of stroke and wait several hours before seeking care, believing that the deficits will go away if they wait long enough. This is perhaps contributed to by the fact that ischemic strokes are typically painless and the symptoms are more difficult to recognize. One study performed in 1993 [3] found that the mean time between symptom onset and physician contact was 13.4 h, with a median of 4 h. Community awareness forums have been successful in educating certain populations about the need to recognize stroke symptoms and activate emergency medical services. Following a public awareness project in Durham, NC, USA 86% of patients with cerebral infarction presented to the hospital within 24 h of symptom onset, compared with 37% before their educational efforts [4]. Communities should be informed that the five most common symptoms of stroke include: (1) sudden numbness or weakness of face, arm, or leg, especially on one side of the body; (2) sudden confusion, trouble speaking, or understanding; (3) sudden trouble seeing in one or both eyes; (4) sudden trouble walking, dizziness, loss of balance, or coordination; and (5) sudden severe headache with no known cause.

The use of the Emergency Medicine System is also crucial in the early treatment of stroke. Proper training of the paramedics allows these frontline personnel to obtain crucial information from the family or other bystanders. This includes time of onset (or time patient was last seen to be normal) and medications the patient might be taking. This historical information, as well as physical findings such as aphasia, motor deficit, and vital signs, can be called to the hospital emergency department so that a stroke alert protocol can be activated, saving significant time in treatment.

## *Stroke Recognition in the Emergency Room*

Chapter 1 reviews major considerations used to identify whether a patient is suffering from a stroke (versus a stroke mimic, such as a multiple sclerosis attack, migraine aura, or a partial seizure) and differentiating ischemic stroke from hemorrhagic stroke or cerebral venous thrombosis. Generally, ischemic stroke will present with the sudden onset of neurological dysfunction which may involve any or all of the following: weakness, numbness, vision

loss, diplopia, dysarthria, gait disorder, aphasia, lightheadedness, vertigo, or disturbed level of consciousness. While a headache can occur with ischemic stroke (up to 10% of cases, especially if arterial dissection is present), it is more suggestive of hemorrhagic stroke, migraine, or cerebral venous thrombosis. Positive neurological phenomena (extra movements, flashing lights in vision, paresthesias) are much more suggestive of migraine aura or seizure than of ischemic stroke. Since ischemia can co-occur with migraine or seizure, identifying migraine or seizure does not exclude ischemia.

## *Ischemic Stroke Types*

Patients suffering from ischemic strokes often have symptoms and signs that suggest which arterial distribution is involved. One should always attempt to match a patient's presentation with these common stroke presentations. Ischemia within major arterial territories (anterior cerebral artery, middle cerebral artery, posterior cerebral artery, basilar artery, and vertebral arteries) have typical associated patterns of signs and symptoms. Patterns associated with small, deep strokes (lacunar strokes) should also be considered.

### Anterior Cerebral Artery (ACA)

Patients experience ACA occlusion uncommonly (only 3%) compared to other ischemic stroke types. Weakness of the contralateral leg, with possibly some mild arm weakness, is the hallmark of the presentation. Patients may also have deviation of gaze towards the side of the lesion. Other frontal lobe symptoms include amotivational states (abulia, akinetic mutism), memory disturbance, emotional disturbances, paratonia (a tendency to resist movement of limbs in any direction), and a particular type of aphasia (transcortical motor) that presents as intact repetition and comprehension, but poor naming and fluency. In some cases, if the ACA is occluded very proximally, the recurrent artery of Heubner is affected; this can cause infarction of the anterior limb of the internal capsule, adding face and arm weakness (without sensory loss) to the clinical presentation. If the patient presents only with weakness of face, arm, and leg – it may be difficult to distinguish such a patient, on clinical grounds, from a pure motor lacunar infarction (see Lacunar Syndromes below).

### Middle Cerebral Artery (MCA)

MCA infarcts can be devastating, and the degree of impairment will depend on how much and what portions of the MCA are occluded. General features

of these infarctions include contralateral hemiplegia (most often, the face and arm are much weaker than the leg), conjugate eye deviation to the side of the infarction, and contralateral sensory loss. If the infarct is in the dominant hemisphere (the left hemisphere in 99% of right-handed patients) then global (receptive and expressive) aphasia may result. If the upper division only of the MCA is occluded, an expressive (Broca's) aphasia may result while the lower division may result in a receptive (Wernicke's) aphasia. Patients may also experience a curious contralateral attentional deficit, most commonly with non-dominant hemisphere lesions. This neglect phenomenon involves poor awareness of the contralateral side, which may include the patient's own body (lack of recognition that it is their own), side of space (inability to pay attention to objects on that side of the body), or lack of awareness that they have suffered a stroke (anosognosia). To confuse matters somewhat, if the MCA is occluded very proximally, then smaller penetrating arteries (lenticulostriate arteries) supplying the ipsilateral basal ganglia are occluded. This leads to superimposed lacunar-type infarctions that add to the patient's presenting deficits, and may complicate the process of localization. Occlusion of these penetrating arteries causes a larger region of infarction, thereby increasing the likelihood of mass effect related to edema.

### Posterior Cerebral Artery (PCA)

PCA occlusions have highly variable effects, depending on the portion of artery involved. Distal segment occlusions may lead to homonymous (both eyes) contralateral superior or inferior quadrant vision loss (a quadrantanopsia). Infarctions inferior to the calcarine fissure of the striate cortex will lead to a superior quadrantanopsia; infarctions superior to this location will cause an inferior quadrantanopsia. Infarctions of both areas will lead to a complete homonymous hemianopsia. More proximal occlusions can also affect the deep penetrating arteries that supply the midbrain and thalamus as well as the branch that supplies the medial temporal lobe. A complete discussion of the variety of presentations is beyond the scope of this text, but here some common presentations are described. Infarctions of the thalamus often cause contralateral sensory loss, sometimes with the subsequent development of chronic pain (thalamic pain syndrome). If both thalamii are affected, confusion and severe disruptions in the level of consciousness may occur. Midbrain lesions may lead to dysconjugate gaze, hemiplegia, or even stupor and coma. If the subthalamic nucleus is involved, movement disorders such as hemiballismus or hemichoreoathetosis may occur. Complete occlusion of the PCA may lead to memory impairment or to unique cortical dysfunctions such as an inability to read (alexia), to name (anomia), or to identify viewed objects (visual agnosia).

### Basilar Artery (BA) and Vertebral Arteries (VA)

The most dramatic presentation of BA disease, due to proximal occlusion, is rapid onset coma. It is important to consider this possibility in the early differential diagnosis of coma. BA occlusion at any level, depending on collateral pathways (especially the presence of posterior communicating arteries), can lead to unilateral or bilateral PCA infarctions. Below the PCA arteries, in descending order, are the superior cerebellar arteries (SCA), anterior inferior cerebellar arteries (AICA), and finally the posterior inferior cerebellar arteries (PICA). A detailed description of the common presentations associated with occlusion of these large arteries is beyond the scope of this text. In general, ischemia due to compromise of the BA or VA can present with brainstem signs such as global depression of consciousness, vertigo, ataxia, nystagmus, nausea, vomiting, gaze palsies, and loss of facial sensation. Loss of facial sensation on one side, with contralateral loss of body sensation (crossed sensory findings) is highly suggestive of a brainstem lesion. A Horner's syndrome (ptosis, miosis, and anhydrosis on one side) may also occur with brainstem infarcts.

### Lacunar Syndromes

Often infarctions are due to occlusion of small penetrating arteries within the brain. These infarcts are generally small (1.5 cm diameter or less) and are located deep within the brain. Common locations for lacunar infarctions are the basal ganglia, thalamus, internal capsule, cerebellum, and brainstem. The recognition of common lacunar syndromes can guide the early treatment of ischemic stroke patients, may aid in localization, and will help with prognostication. In general, recovery from lacunar infarctions occurs more rapidly and more completely than from large artery ischemic strokes and are associated with less mortality. The five most common lacunar syndromes are described as follows:

(a) Pure motor: This involves contralateral (to the stroke) weakness affecting, roughly equally, face, arm, and leg. Facial weakness is sometimes absent. Infarct locations commonly associated with this syndrome include: corona radiata, internal capsule, pons, or medullary pyramid.
(b) Ataxia hemiparesis: This involves any combination of weakness and poor coordination on the same side of the body. The poor coordination should be 'out of proportion' to the degree of weakness. Common sites associated with this presentation include the anterior limb of the internal capsule and the corona radiata.
(c) Clumsy-hand dysarthria: This involves severe slurring of speech, with mild hand weakness as well as hand dyscoordination. Sometimes weakness of the arm or leg is present. The pons is the most likely localization for this infarct, although an internal capsule lacune may also cause these symptoms.

(d) Pure sensory: This presents as sensory loss affecting, roughly equally, the contralateral face, arm, and leg. The infarct is typically in the thalamus, although other locations have been reported.
(e) Mixed sensory motor: This is the combination of pure sensory and pure motor lacunar syndromes. These can result from infarcts involving the thalamus, internal capsule, basal ganglia, or pons. These infarcts tend to be larger than those associated with other lacunar syndromes.

## *A Word About Tissue Plasminogen Activator (tPA)*

Recombinant tissue plasminogen activator (rt-PA) is chemically similar to endogenous tissue plasminogen activator (tPA). tPA is a serine protease which converts plasminogen to plasmin, a fibrinolytic enzyme (Fig. 2.1). Upon administration, recombinant tPA increases plasmin enzymatic activity, resulting in fibrinolysis. It is often referred to as a "clot buster" and is used to dissolve a clot with restoration of blood supply to an area of cerebral ischemia.

Tissue plasminogen activator (rt-PA) was approved by the FDA in 1996 for the treatment of acute ischemic stroke based on the findings of the 1995 NINDS stroke trial [5]. This double blind placebo controlled trial demonstrated that patients treated with rt-PA within 3 h of symptom onset had a 30% greater likelihood of having minimal to no disability 90 days following treatment compared to a placebo treated group. There was a 6.4% risk of symptomatic intracerebral hemorrhage in the rt-PA treated group compared to 0.6% in the placebo group. However, even considering the risk of bleeding, the mortality at 90 days was 21% in the placebo group and only 17% in the rt-PA group.

Although the NINDS trial demonstrated improvement within a 3-h time frame (compared to placebo) patients have even better outcomes if treated earlier. This is demonstrated in Fig. 2.2.

Therefore, if appropriate, the administration of IV tPA (and, indeed, the management of acute stroke overall) should be carried out expeditiously.

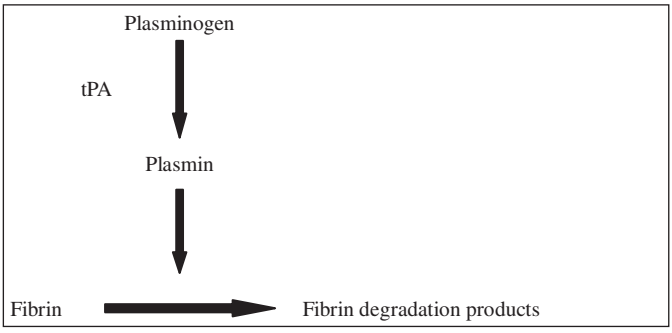


**Fig. 2.1** Mechanism of tPA action

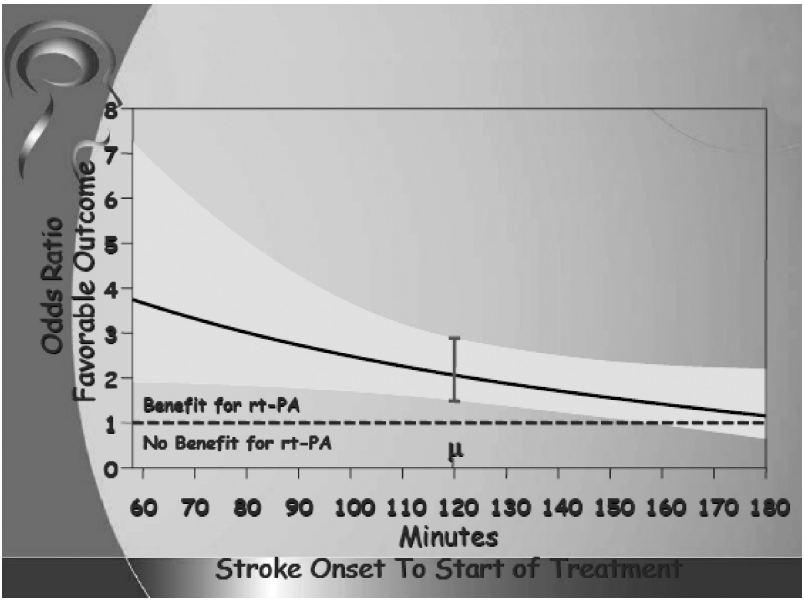


**Fig. 2.2** NINDS TPA stroke study parts 1 and 2. Relation of time to treatment to odds ratio of favorable outcome. (Marler, JT et al. Neurology 2000: 55, 1649–1655)

## Emergency Department Management of Ischemic Stroke

As with any acutely ill patient, a stroke patient should first undergo assessment of airway, breathing adequacy/oxygenation, and circulation with subsequent correction of any discovered problems. Because of the importance of timely intervention in treating patients with stroke, it is beneficial if not imperative that hospitals develop a set of orders outlining the protocol to be followed when a stroke patient arrives. If the patient is transported by emergency medicine services, the hospital can institute the protocol immediately. Several capabilities should be available in the emergency department including the timely interpretation of studies and the availability of neurosurgical intervention should the patient develop symptomatic intracranial hemorrhage.

### *Rapid Testing*

The laboratory should be available to perform the following blood tests immediately: PTT, INR, blood glucose, and CBC with platelet count. As it may take time to process these studies, obtaining them early reduces the time to treatment. Blood should be drawn and sent to the lab prior to head CT. The head CT scan should be performed as soon as possible to exclude a hemorrhagic stroke.

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Level of Consciousness** | 0 Alert<br>1 Drowsy<br>2 Stuperous<br>3 Coma | | | | | | | | |
| **LOC** | 0 Answers Both Correctly<br>1 Answers One (1) Correctly<br>2 Incorrect | | | | | | | | |
| **LOC** | 0 Obeys Both Correctly<br>1 Obeys One (1) Correctly<br>2 Incorrect | | | | | | | | |
| **Best Gaze** | 0 Normal<br>1 Partial Gaze Palsy<br>2 Forced Deviation | | | | | | | | |
| **Visual** | 0 No Visual Loss<br>1 Partial Hemianopia<br>2 Complete Hemianopia<br>3 Bilateral Hemianopia Blind | | | | | | | | |
| **Facial Palsy** | 0 Normal<br>1 Minor<br>2 Partial<br>3 Complete | | | | | | | | |
| **Motor Arm** | 0 No Drift<br>1 Drift<br>2 Some Effort Against Gravity<br>3 Limb Falls<br>4 No Movement | R | L | R | L | R | L | R | L |
| **Motor Leg** | 0 No Drift<br>1 Drift<br>2 Some Effort Against Gravity<br>3 Limb Falls<br>4 No Movement | R | L | R | L | R | L | R | L |
| **Limb Ataxia** | 0 Absent + = Present<br>1 One (1) Limb - = Absent<br>2 Two (2) Limbs<br>Score → | R<br>U<br>L<br>**Total:** | L | R<br>U<br>L<br>**Total:** | L | R<br>U<br>L<br>**Total:** | L | R<br>U<br>L<br>**Total:** | L |
| **Sensory** | 0 Normal<br>1 Mild to Moderate Loss<br>2 Severe to Total Loss | | | | | | | | |
| **Best Language** | 0 Normal<br>1 Mild to Moderate Aphasia<br>2 Severe Aphasia<br>3 Mute | | | | | | | | |
| **Dysarthria** | 0 Normal<br>1 Mild to Moderate<br>2 Severe | | | | | | | | |
| **Extinction/ Inattention** | 0 Normal<br>1 Partial Neglect<br>2 Complete Neglect | | | | | | | | |
| **Total / Initial:** | | | | | | | | | |

**Fig. 2.3** The NIH Stroke Scale

The CT scan may also demonstrate subtle early signs of infarction. Although the presence of these signs is associated with a poor outcome, this does not preclude the use of rt-PA unless there is evidence of hemorrhage. The scans are generally performed without contrast unless there is reason to suspect a tumor.

## *The NIH Stroke Scale*

Evaluation of the patient should also include performance of the NIH stroke scale (Fig. 2.3). Training for this as well as certification for performing the evaluation can be obtained through several routes including accessing the American Stroke Association website. Initially utilized in research trials, this 15-item scale has proven valuable in quantifying the deficits of the stroke patient and can be useful when discussing the patient's condition with the treating neurologist. It is also beneficial in following the patient in the hospital

to assess improvement or deterioration in neurological condition. (It does have some limitations in that it does not capture brainstem deficits well. For example, palatal weakness is not scored on this scale, but a lesion associated with dysphagia secondary to a stroke can be quite disabling).

## *Deciding Whether to Administer IV tPA*

First, accurately establish the time of symptom onset. If a patient's symptoms have been present for less than 3 h, many criteria must be reviewed prior to tPA administration. These are listed in Fig. 2.4.

Glucose must be measured since hypoglycemia can be associated with a focal neurological deficit that is reversible with glucose administration. PTT, INR, and platelet count must be obtained to prevent the use of thrombolytic therapy in patients with coagulation defects. By obtaining these lab values soon after the patient arrives in the emergency department, treatment delays can be avoided.

## *Caveats and Special Considerations*

While the judgment of the treating physician, based on other studies or special circumstances, may allow for the bending of some rules (such as treating

**If any of the following are answered YES, Patient may NOT receive tPA:**

| | | |
|---|---|---|
| Yes | No | Stroke Symptom onset more than 3 hours (Last time patient was known to be without stroke symptoms) |
| Yes | No | Age 18 or younger |
| Yes | No | Comatose or unresponsive |
| Yes | No | Stroke Symptoms clearing spontaneously. Stroke symptoms minor and isolated. |
| Yes | No | Intracranial/Subarachnoid hemorrhage (SAH). Clinical history suggestive of SAH even if CT negative |
| Yes | No | Active internal bleeding or acute trauma (fracture) on examination |
| Yes | No | INR greater than 1.7 |
| Yes | No | Platelet count less than 100,000 |
| Yes | No | Glucose less than 50 |
| Yes | No | HTN uncontrolled despite medication with Systolic BP greater than 185 or. Diastolic BP greater than 110 |

History of:

| | | |
|---|---|---|
| Yes | No | Active malignancy |
| Yes | No | Recent MI or pericarditis within the past 3 months |
| Yes | No | Recent arterial puncture at noncompressible site within previous 7 days (such as subclavian) |
| Yes | No | Lumbar puncture within 3 days |
| Yes | No | History of GI or urinary hemorrhage within 21 days |
| Yes | No | Pregnancy, lactation, or childbirth within 30 days |
| Yes | No | History of Intracranial hemorrhage |
| Yes | No | Major surgery or serious trauma within in last 14 days |
| Yes | No | Seizure with postictal residual neurological impairment . |
| Yes | No | Major ischemic stroke or head trauma within the last 3 months |
| Yes | No | Heparin within 48 hrs with PTT greater than upper limits of normal |
| Yes | No | Known AV Malformation or aneurysm |
| Yes | No | Known bleeding disorder |

**Fig. 2.4** Criteria for tPA Administration

someone under the age of 18) it should be noted that non-adherence to these guidelines (especially as regards a well-defined time of stroke onset and control of elevated blood pressure) has led to poorer outcomes. In a multi-hospital survey in Cleveland, a higher rate of symptomatic hemorrhages and a high-mortality rate were found in those treated with tPA [6]. An analysis of those treated in the Cleveland area found multiple protocol violations, especially as regards carefully establishing a time of onset of symptoms and treatment with tPA despite blood pressures being higher than the protocol allows. A follow-up study, also surveying Cleveland area hospitals, showed that after improved adherence to the guidelines, good outcomes similar to those of the original NINDS trail were obtained [7].

The determination that a neurological deficit is rapidly improving has been somewhat problematic. Improvement over the baseline NIH score is not considered rapid improvement if the patient continues to have a significant deficit. A good rule of thumb has been to assume the patient is not going to show further improvement in his condition. Is the deficit mild enough that he can continue to function at a high level? Even mild weakness might be devastating to an individual whose occupation depended on fine motor movements, so rt-PA would be a consideration in that patient even with a low NIHSS value. On the other hand, in the NINDS trial, patients with too high of an NIHSS value (greater than 23) tended to do poorly with IV tPA administration and physicians can reasonably withhold tPA under these circumstances.

If a patient's blood pressure is prohibitively elevated for tPA administration (greater than or equal to 185/110 mmHg) it is permissible to lower the blood pressure with various agents so that tPA can be administered. Acceptable agents for this purpose include IV labetolol, IV hydralazine, or IV nicardipine. Lowering a patient's blood pressure more than 15%, for this purpose, is generally not recommended [8].

## *Beyond the 3-h Time Frame*

It should be noted that patients who are suffering from an ischemic stroke, who are considered ineligible for tPA or who are beyond the 3-h time frame, should be considered for other interventions (to be described below). Hospitals which do not themselves have the capability of performing these procedures should emergently contact hospitals which do, in order to arrange for immediate transfer of the patient if deemed appropriate.

Some studies have indicated that intra-arterial thrombolytic therapy may be beneficial in the patient who is treated within 6 h of symptom onset (PROACT I and II) [9, 10]. tPA is typically the agent of choice used in practice. Intra-arterial therapy involves the use of an intra-arterial catheter to instill a small-tPA dose that is concentrated at the level of the arterial occlusion. With basilar artery occlusions, because of its very poor natural history, patients may be treated up to 24 h or longer after symptom onset.

Additional acute therapies are also available. Mechanical catheter retrieval devices, which physically remove thrombus, have been approved for use in restoring cerebral flow in patients with occlusion of a major intracerebral artery. Some such devices are FDA approved for use within 6 h of an ischemic stroke. Although some patients have had remarkable recovery utilizing these procedures, one must be aware of the risks involved. The Safety and Efficacy of Mechanical Embolectomy in Acute Ischemic Stroke Trial [11] demonstrated 48% recanalization rate with the MERCI (Mechanical Embolus Removal in Cerebral Ischemia) catheter. Because the MERCI trial did not have a placebo group for direct comparison, this can be compared to only 18% recanalization for the placebo group in the PROACT II trial. However, the mortality rate for use of the catheter was 43.5% in the treated group at 90 days compared to 27% in the placebo group of the PROACT II trial. Many stroke neurologists would only consider mechanical clot retrieval in patients who are deemed inappropriate for tPA. Both mechanical retrieval and intra-arterial thrombolysis are limited to facilities that have immediate access to cerebral angiography and the availability of trained neurointerventionalists.

## Inpatient Care

All patients should undergo an EKG on the first day of admission and should undergo telemetry monitoring for at least the first 24 h of admission. The continued management of patients who have been treated with tPA, or those who were not candidates for the medication, is important in achieving optimal outcomes. Among the parameters to consider are blood pressure, fluid balance, glucose, anticoagulation, and platelet inhibition.

### *Blood Pressure*

If tPA is administered, the patient must be monitored for at least 24 h in an intensive care setting. Vital signs should initially be checked every 15 min after tPA administration, for the first 30 min. Thereafter, vitals are checked every 30 min for the next hour and then every hour for the following 16 h. . Blood pressure parameters and treatment protocols should be standardized. The present recommendations, for the first 24 h post-tPA, are to keep systolic BP below 185 mmHg and diastolic below 110 mmHg. Labetolol, hydralazine, or nicardipine are the best agents to lower blood pressure in this setting. A lower limit for diastolic blood pressure of 60 mmHg should be used.

Twenty-four hours after tPA administration, and immediately for patients who did not receive tPA, blood pressure is typically allowed to run higher. The reason for this approach is the frequent loss of cerebral autoregulation. Cerebral autoregulation in the normal state results in steady cerebral blood flow for

mean arterial pressures between 60 and 160 mmHg. However, autoregulation is often lost in the acute stroke setting, and as a result, decreasing blood pressure will often decrease cerebral blood flow. Unless there is a cardiac, renal or other medical reason that the pressure needs to be lowered, the current recommendation is to lower the blood pressure only if it is above 220/120 mmHg. Agents such as sublingual nifedipine, that lower the blood pressure quickly, should be avoided. A reasonable decrease in blood pressure would be 15% over 24 h. For patients who have preexisting hypertension, it is generally agreed that antihypertensive medications should be restarted after 24 h if patients are neurologically stable unless a specific contraindication to restarting treatment is known. In cases of larger strokes, where the peak effects of edema may cause elevations in intracranial pressure or herniation syndromes, delaying use of antihypertensives until past the time of peak edema, is considered prudent.

## *IV Fluids*

Hypotonic and glucose containing intravenous fluids are not recommended in the acute setting of cerebral infarction. Cytotoxic edema resulting from cellular membrane disruption with resulting swelling of the cell body develops with infarct. The use of these solutions can increase the cellular damage with influx of water into the cell. Normal saline is therefore generally utilized in these patients.

## *Glucose*

Euglycemia should be the clinical goal in the setting of stroke. In addition to the negative effects of hypoglycemia for stroke outcome, it has also been noted that patients with sustained glucose greater than 140 mg/dL have less favorable stroke outcomes [12, 13]. Glucose levels should be monitored and, if found to be greater than 140–180 mg/dL, treatment with insulin is indicated.

## *Anticoagulation*

The use of anticoagulation in acute ischemic stroke is controversial. The present clinical recommendations are to avoid anticoagulation in the acute phase (the first few weeks) of stroke. Present data does not indicate that the use of heparin or heparinoids in the acute management of stroke results in a decrease in the risk of early recurrence of stroke. However, there is an increased risk of conversion to a symptomatic hemorrhagic stroke with the use of anticoagulation, especially in patients with moderate- to large-sized strokes. An example of this is seen in Fig. 2.5. This recommendation also holds for strokes felt to be of cardioembolic origin, such as in the setting of atrial fibrillation. No subgroup or arterial distribution has been identified in which anticoagulation has

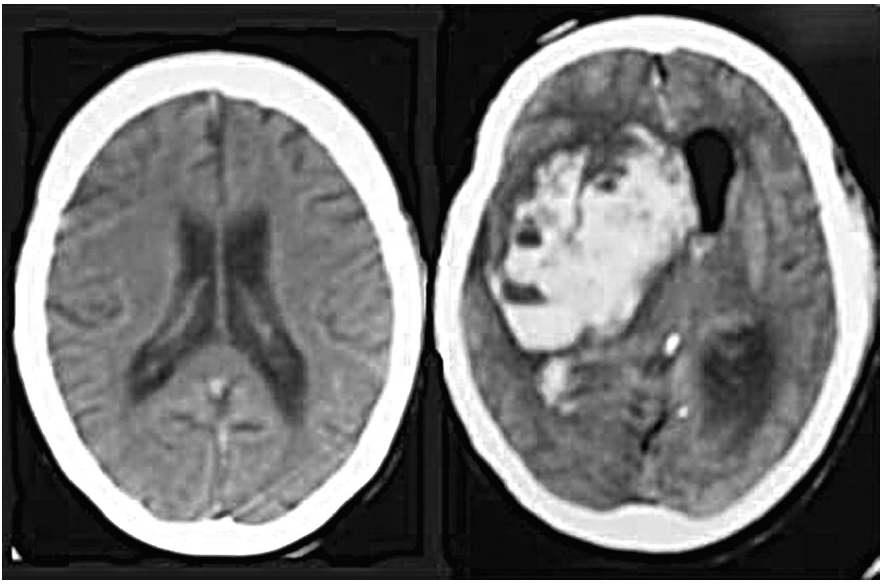

**Fig. 2.5** Patient presents at 10 A.M. with left hemiparesis and scan on left is obtained. Heparin was started. At 4 P.M. patient becomes obtunded and scan on right is obtained, showing large hemorrhage (*See* Color Insert)

demonstrated a significant benefit in the setting of acute stroke, due to the concomitant increased risk of bleeding. (Exceptions might include the use of anticoagulation in the setting of cerebral venous thrombosis. It is also common, though unproven, to use anticoagulation in the setting of large artery dissections with presumed embolic ischemic strokes.) Anticoagulation of any form (and antiplatelet therapy) should not be utilized within 24 h of tPA administration.

## *Platelet Inhibition*

Aspirin is the only antiplatelet agent studied showing benefit in the acute management of stroke. Two large trials have been performed. When the results of the Chinese Acute Stroke Trial and the International Stroke Trial were combined, a modest benefit was obtained [14]. This has led to the recommendation of instituting aspirin at a dose of 325 mg per day within the first 48 h after stroke. The use of aspirin is not recommended within 24 h of rt-PA administration. A 2007 published study by Kennedy et al. [15] compared clopidogrel plus aspirin to aspirin alone given within 24 h of stroke onset. There was a 7% recurrent stroke incidence in the combined group compared to 11% in the aspirin group. However, this did not reach statistical significance. Other trials, such as the MATCH trial, have found double the risk of significant bleeding

when using aspirin plus clopidogrel compared to clopidogrel alone [16]. Hence combined use of these two antiplatelet agents is not recommended for acute stroke treatment.

## Preventing and Treating Stroke Complications

### *Deep Venous Thrombosis (DVT)*

Stroke patients frequently have deficits that impair their ability to ambulate safely or that may cause them to be confined to bed. This limitation in mobility can lead to a deep vein thrombosis (DVT) and subsequently to a pulmonary embolism; therefore, measures should be taken to prevent this complication. The heparinoid enoxaparin appears to be quite effective in this setting. A study by Sherman et al. indicated a 43% improvement in venous thromboembolism with patients treated with enoxaparin given 40 mg subcutaneously once a day compared to subcutaneous unfractionated heparin [17]. The risk of intracerebral hemorrhage with the use of low dose anticoagulants appears to be low [18]. Sequential compression devices may also be used to prevent deep vein thrombosis especially in patients who have a contraindication to anticoagulation. Additionally, early mobilization of patients and the early involvement of physical therapists helps to prevent DVTs and improves stroke outcomes.

### *Infection Prevention and Treatment*

One of the major dangers following stroke is aspiration, which may be silent, resulting in aspiration pneumonia. Therefore patients should be kept NPO until a swallow screening evaluation can be performed. The presence of a gag reflex does not guarantee that swallowing is safe. A video swallowing study may be necessary in some patients. If the patient is at aspiration risk, gastric feeding tubes are often utilized. Multiple day use of in-dwelling foley catheters should also be avoided, since this carries a high risk of urinary tract infections (UTIs).

If an infection does occur, aggressive treatment is the rule. Antibiotics should be administered early to control infection and use of acetaminophen and other measures to control fever. A clear correlation between fever and worse stroke outcomes has been established [19, 20].

### *Cerebral Edema*

As mentioned earlier, cerebral edema can cause significant morbidity and mortality due to increased intracranial pressure, local pressure effects causing obstructive hydrocephalus, further infarction due to pressure on adjacent

arteries, or herniation of brain into other compartments. Edema may become maximal anywhere between 24 and 96 h after ischemic stroke onset. An emergent CT scan should be performed if a patient worsens neurologically. Emergent neurosurgical consultation may be indicated to consider placement of an intraventricular drain (in the case of hydrocephalus). Decompressive surgery must be considered in the case of cerebral edema with impending herniation syndrome [21] (most typically due to MCA or ICA occlusion in a young patient) or in cases of large cerebellar infarctions with significant edema. The use of corticosteroids for treatment of cerebral edema in stroke is not recommended. Complications such as increased glucose levels and infections may be aggravated by steroids. Reasonable measures to reduce intracerebral pressure are reviewed in Chapter 4 and include intubation with hyperventilation and use of osmotherapy (such as IV mannitol). These measures, while logical, are generally considered 'last ditch' efforts to save the life of the patient. Data regarding their effects on mortality and neurological outcome are mixed.

### *Hemorrhagic Transformation*

A region of cerebral ischemia may 'transform' into a region of superimposed hemorrhage. This may be only petechial hemorrhaging and therefore be of no clinical significance. More significant confluent regions of ischemia may not require further changes in therapy. Frank hemorrhage, beyond the area of infarction, with associated mass effect and clinical deterioration, occurs in as many as 10% of ischemic strokes, and would significantly complicate management, possibly even requiring surgical evacuation. For further information regarding management of these hemorrhages, see Chapter 4.

## In-Patient Testing for Stroke/TIA Etiology

The treating physicians should search for stroke etiologies, especially those that will affect immediate management, expeditiously during the patient's hospitalization. In the majority of cases, it is most useful to order a standard in-patient work up (hopefully as part of an available order set) immediately upon admission.

TIA patients should also undergo admission and a rapid work up, if the event occurred within 3 days. Following a TIA, 10.5% of patients will have a stroke within 90 days with 50% of these occurring within 2 days of the TIA. Twenty-one percent of these strokes are fatal with another 64% resulting in disability [22]. TIAs, therefore offer an opportunity to intervene and prevent a significant number of strokes. Indeed, two European studies [23, 24], have found that early evaluation and management can decrease the risk of stroke in the 90-day period by 80%.

Risk factors for TIA and ischemic stroke include hypertension, atrial fibrillation, carotid stenosis, cardiomyopathy, hyperlipidemia, vasculitis, cigarette smoking, hypercoaguable states, diabetes, syphilis, elevated C-reactive protein, and elevated homocystine levels, among others. Much of the work-up for TIA and ischemic stroke is a 'plumbing' evaluation, meaning that the etiology of a stroke can be anywhere from the heart through the 'pipes' that lead to the site of the stroke. It is therefore mandatory to image all of these regions. Standard evaluations and reasons for testing include the following:

- Brain MRI – This may provide significant additional information including the existence of a stroke not detected on head CT, the detection of patterns of ischemia that could suggest an etiology (for example, infarctions in multiple arterial territories, suggestive of embolic disease), and an indication of the acuity of the infarcts.
- Imaging of intracranial and extracranial vasculature – Modalities include Magnetic resonance angiography (MRA), CT angiography (CTA), carotid duplex, transcranial doppler (TCD), or cerebral catheter arteriography. If a patient will already be getting an MRI of the brain, MRA of the head and neck is typically ordered at the same time. CT angiogram of the head and neck vessels is also reasonable, and is performed by some emergency departments as part of their ischemic stroke protocol. The intracranial portion of this testing can identify important information such as extensive atherosclerotic disease, vascular occlusions, or evidence of cerebral vasculitis. Extracranial imaging is important to identify carotid atherosclerotic disease with stenosis or arterial dissections. Carotid ultrasound has a sensitivity for significant stenosis of approximately 85% compared to digital arteriography. In combination with MR angiography, the sensitivity of detecting carotid stenoses is close to 100%. CT angiography is also helpful in assessing for carotid stenosis with a sensitivity of 88–98%, depending on the study. If a question remains regarding the degree of stenosis, catheter arteriography may be necessary. Dissections are most effectively imaged by catheter angiography, but they can also be evaluated by CT or magnetic resonance angiography.
- Transthoracic echocardiogram (TTE) – This can identify embolic stroke sources including cardiac thrombus, enlarged left atrium (a risk factor for the development of atrial fibrillation), patent foramen ovale (PFO), atrial septal aneurysm, endocarditis, or very low ejection fraction. If a 2D-echocardiogram does not suggest an ischemic stroke cause or is of poor quality, and clinical suspicion remains high that an event was cardioembolic in origin, a transesophageal echocardiogram (TEE) should be performed. TEE is more effective in identifying left atrial appendage thrombus, aortic artery disease, and has better overall resolution. Transcranial Doppler studies implementing a bubble test are also useful for PFO detection.
- Blood work – Blood testing should be driven by clinical suspicion. Commonly performed blood tests for all ischemic stroke patients include

complete blood count (CBC) with differential, erythrocyte sedimentation rate (ESR), blood urea nitrogen (BUN), serum creatinine, prothrombin time (PT), activated partial thromboplastin time (aPTT), blood glucose, hemoglobin A1c, fasting lipid profile, RPR, and FTA. Evidence of or suspicion for atherosclerotic disease may also prompt testing for C-reactive protein and homocysteine levels. Suspicion for a hypercoagulable state might prompt much more extensive testing (see Chapter 10 regarding appropriate blood work). Fever with concern for endocarditis should prompt multiple blood cultures. Suspicion for rare disorders such as CNS vasculitis is beyond the scope of this chapter but will include testing for measures of inflammation, infection, and autoimmune disease.

## Beginning Preventative Treatment in the Hospital

Many preventative measures should be instituted while the patient is still hospitalized (for a fuller discussion of all long-term preventative measures, see Chapter 3). Basic preventative measures to consider include: control of chronic hypertension, anticoagulation for atrial fibrillation, surgical or endovascular treatment of carotid artery stenosis, cholesterol control, smoking cessation, and use of an antiplatelet medication (if the patient is not on anticoagulation).

### *Hypertension*

Blood pressure may be transiently elevated following a TIA or stroke and often decreases spontaneously. However, in sustained hypertension the long-term risk of stroke increases significantly. Lowering a patient's blood pressure has been proven to be effective in lower stroke risk by 30–40% in meta-analyses of randomized controlled trials [25,26]. Therefore tight control of blood pressure, in the long term, is recommended. Starting an antihypertensive while the patient is still in the hospital is reasonable and often leads to improved long-term compliance. While a normal blood pressure of $<120/80$ mmHg would be ideal, the appropriate goal for each patient must be individualized.

### *Atrial Fibrillation*

Atrial fibrillation may produce a cardioembolic source of cerebral ischemia. This risk increases with age and comorbid conditions such as congestive heart failure, hypertension, and diabetes. The use of warfarin decreases ischemic stroke risk by 68% in older age groups [27]. Aspirin decreases the risk slightly, but is significantly less effective than warfarin. There is no data to support the use of combination therapy using warfarin together with aspirin or other antiplatelet agents. In cases of atrial fibrillation and TIA, anticoagulation can

be started while the patient is hospitalized, and this would generally be recommended. In cases of moderate to large strokes, anticoagulation can reasonably be delayed for 2–4 weeks to prevent symptomatic hemorrhagic conversion.

## *Carotid Artery Stenosis*

In patients with symptomatic carotid stenosis of greater than 70%, the North American Symptomatic Carotid Endarterectomy Trial [28] found that carotid endarterectomy reduced the risk of ipsilateral stroke to 9% after 2 years, compared to 26% in the medical management arm. The greatest benefit occurred when surgery was performed within 2 weeks of symptom onset. There was no significant difference between the two groups for less severe stenosis. In general, for patients with ipsilateral ischemic stroke or TIA, and at least 70% carotid stenosis, CEA should be strongly considered. The surgical/arteriographic risk for these procedures, in the study, was less than 3%. For patients who are at higher risk of complications due to concurrent medical conditions compared to those in the study, the benefits of endarterectomy compared to medical therapy would be less robust and medical management might be preferable. For patients with contraindications to surgery, such as prior radiation treatment to the neck or lesions that cannot be approached surgically, carotid stents have been approved to manage the stenosis. For a more detailed analysis of carotid stenosis and indicated therapy, please see Chapter 11.

## *Hyperlipidemia*

Hyperlipidemia is a risk for cardiovascular disease and to a lesser degree cerebrovascular disease. The current recommendations call for an LDL value of less than 100 mg/dL in patients who have had cerebral ischemic events. If there are multiple ischemic stroke risk factors, an LDL of less than 70 mg/dL is recommended. Statin agents have been shown to decrease the risk of stroke. This may not be solely on the basis of cholesterol control as they also have anti-inflammatory properties and have been discovered to lower C-reactive protein levels (a known stroke risk factor). Statins should be initiated during stroke or TIA admissions to improve long-term compliance.

## *Smoking Cessation*

Cigarette smoking is a major modifiable risk factor. All smokers should receive counseling and education regarding the importance of smoking cessation. Several agents and techniques are available to help patients with this endeavor.

### *Antiplatelet Medication*

The use of antiplatelet agents decreases the risk of recurrent stroke. Aspirin has been shown to decrease the risk of stroke by 18% compared to placebo [29, 30]. Clopidogrel (Plavix) has a relative risk reduction that is 8% better than aspirin, using a combined endpoint of stroke, myocardial infarction, and peripheral vascular arterial events [31]. Controlled release dipyridamole plus aspirin (Aggrenox) has been shown to lead to a decreased stroke rate that is 23% better than aspirin and 37% better than placebo [32]. The use of these agents, in patients who are not anticoagulated, therefore is of paramount importance in preventing recurrent stroke.

## Conclusion

The acute management of stroke requires emergent and structured protocols for efficient patient management. When the patient has had an ischemic stroke, early treatment can result in improved clinical outcomes. Proper medical management, even in patients who are not candidates for thrombolytic or neurointerventional procedures, results in better outcomes. Studies have demonstrated a significant decrease in the number of patients with severe disability when they are treated on a dedicated stroke floor, compared to those treated on a general medical ward. Many hospitals are now becoming certified as Primary Stroke Centers, and accreditation for these programs has been established.

The timely evaluation of transient cerebral ischemia must be stressed. Patients should not be discharged from an emergency department to be evaluated in a few days by their primary care physician. Admission of the patient for observation to obtain the necessary testing within 24 h is recommended. With the high incidence of early stroke after TIA, the use of rt-PA might be facilitated by the admission as well. The development of dedicated clinics that allow for the immediate evaluation of a patient has been possible in some communities. This approach also allows for the timely evaluation and institution of appropriate treatment, but so far is not widely available. With proper care and patient management, the risk of stroke and its devastating effects can be overcome.

## Brief Summary

- Ischemic stroke is commonly the result of arterial occlusion with loss of blood flow to part of the brain, depriving neurons of oxygen and glucose. An event is referred to as a TIA when blood flow is spontaneously restored quickly enough that no neuronal death ensues.
- Treatment of stroke is greatly improved by public recognition of stroke symptoms, a well-coordinated emergency medical service, hospitals with stroke protocols, and a hospital with the capabilities to treat all types of stroke patients and stroke-related complications.

- The symptoms of ischemic stroke or TIA may include the sudden onset of weakness, numbness, vision loss, diplopia, dysarthria, gait disorder, aphasia, lightheadedness, vertigo, or disturbed level of consciousness.
- In order to localize the stroke, it is helpful to be familiar with the usual presentations of large artery occlusions (MCA, ACA, PCA, BA, VA) as well as common lacunar syndromes.
- An acute stroke protocol (see Table 2.1) is helpful in expediting and organizing patient evaluation.
- Deviation from IV/IA tPA protocols can result in poorer outcomes.
- Decisions regarding tPA administration are often complex. In general, patients with severe deficits (NIHSS>23) are unlikely to benefit from tPA. Patients with mild deficits may be offered tPA, even if the NIHSS is low, based on the likely effect of the deficit on that person's life and livelihood. Unless impairment makes this impossible, the patient should be involved in the decision and the patient or family should be aware of the risks and benefits.
- Mechanic retrieval systems (MERCI device) are FDA approved to remove thrombus in the setting of acute stroke (within 6 h), but are not yet well-proven therapies.
- In-patient care should focus on the following:
  - EKG and telemetry monitoring × 24 h
  - Post-tPA patients should have ICU admission with high-frequency assessments

**Table 2.1** Emergency room protocol for suspected ischemic stroke

- Assess airway, breathing adequacy, circulation, vitals
- Rapid Assessment:
  - Determine *time of onset* or time last seen normal
  - Perform *rapid physical* combined with NIHSS
  - Order *stat Head CT* (in some protocols, CTA head/neck also performed)
  - *Draw blood for rapid testing*: CBC, PTT, INR, blood glucose
  - While other testing is underway, obtain *past medical history* and more *detailed history* of current presentation from patient or witnesses.
  - Perform EKG
- When vitals, head CT, neurology exam, and blood results obtained:
  - Review IV-tPA criteria and determine if appropriate for patient.
  - If blood pressure is too high (>185/110 mmHg), consider lowering by 15% or less using IV hydralazine, IV nicardipine, or IV labetolol in order to make patient eligible for IV-tPA.
  - Consent patient (if possible) or family member after explaining regarding risks and benefits of IV-tPA
  - Order IV-tPA if/when appropriate
  - If tPA administered, transfer patient to ICU and use post-tPA order set.
- If patient outside of 3 h IV-tPA window
  - Consider neuroradiology consultation for *IA-TPA or MERCI retriever* if within 6 h window. (Or within 24 h if suspected basilar artery occlusion)

- Blood pressure should be reduced as follows:
  - Within 24 h of tPA
    - SBP <185 and DBP < 110 mmHg
  - No tPA or 24 h after tPA
    - SBP <220 and DBP <120 mmHg
  - Use IV labetolol, nicardipine, or hydralazine to control elevated BP
  - Lower BP at a rate of only 15% per 24 h
- Use only IV normal saline – avoid hypotonic or glucose-containing solutions
- Aim for euglycemia in the hospitalized stroke patient
- There are few acute ischemic stroke cases that will benefit from anticoagulation
- Aspirin is beneficial in acute ischemic stroke

- Preventing and treating stroke complications
  - DVT prophylaxis in the non-mobile patient
    - Use enoxaparin SQ (if not available – use heparin SQ)
    - If neither can be used, apply sequential compression stockings
    - Institute early mobilization and early physical therapy
  - Infection prevention and treatment
    - Patients should be NPO until swallow screening is done
    - Avoid multi-day use of in-dwelling urinary catheters
    - Treat infections early with antibiotics
    - Treat fever with acetaminophen and/or a cooling blanket
  - Cerebral edema and hemorrhagic transformation
    - Obtain emergent head CT in the event of neurological worsening
    - Neurosurgical consultation may be needed for impending herniation syndrome, obstructive hydrocephalus, or hemorrhage with mass effect and neurological worsening
    - Measures to reduce intracranial pressure also include intubation with hyperventilation and osmotherapy (such as IV mannitol)

- See Table 2.2 for in-patient testing for stroke/TIA etiology
- Stroke preventative treatment in the hospital
  - Many preventative measures should be started in the hospital
  - Medicine for chronic hypertension can be started while the patient is still hospitalized
  - Anticoagulation can be started while the patient is still hospitalized in the setting of a TIA.
  - When to start AC in the setting of an ischemic stroke is controversial.

**Table 2.2** In-hospital testing for ischemic stroke/TIA etiology

It is best to order all appropriate tests on the day of admission to avoid delay in treatment or hospitalization. TIA patients, within 3 days of their event, should be admitted to undergo an expedited evaluation.

- Brain MRI (no contrast agent is required unless a tumor is suspected)
- Vascular imaging
  - MRA (with contrast) or CTA of head and neck vessels
  - Carotid duplex is reasonable to:
    - Evaluate carotids in the setting of an anterior circulation ischemic stroke or TIA
    - Confirm a result obtained by CTA or MRA
- Transthoracic echocardiogram (TTE)
  - May add 'bubble study' of PFO detection sought
  - May order transesophageal echocardiogram (TEE) if cardio/aorto-embolic source suspected despite normal TTE.
- Blood testing:
  - Standard testing includes: CBC with differential, ESR, BUN, creatinine, PT, aPTT, blood glucose, hemoglobin A1c, fasting lipid profile, RPR, and FTA.
  - Suspected atherosclerosis: add homocysteine level, C-reactive protein
  - Suspected hypercoagulable state: see Chapter 10
  - Fever with concern for endocarditis: perform multiple blood cultures

- Significant carotid stenosis, if referable to a patient's symptoms, should be treated within 2 weeks of a TIA. CEA is probably a better choice than angioplasty with stenting.
- If significant carotid stenosis is related to an ischemic stroke, many surgeons/interventional radiologists will wait a few weeks before treating to avoid exacerbation of cerebral edema and/or risk of reperfusion hemorrhage.
- If LDL >100 mg/dL (>70 mg/dL if more than one stroke risk factor) then beginning treatment with a statin is indicated.
- Smoking cessation counseling, programs, and medications should be offered to patients who smoke.
- If a patient is not on anticoagulation, they should be discharged on an antiplatelet medication (aspirin, Aggrenox, Plavix).

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http://www.springer.com/978-1-934115-01-5

Stroke Essentials for Primary Care
A Practical Guide
Alway, D.; Cole, J.W. (Eds.)
2009, XII, 204 p., Hardcover
ISBN: 978-1-934115-01-5
A product of Humana Press