COURSE OBJECTIVE: The purpose of this course is to present an up-to-date discussion of acute treatments available for stroke.

LEARNING OBJECTIVES
Upon completion of this course, you will be able to:

- Differentiate between treatments for ischemic and hemorrhagic strokes
- Discuss thrombolytic drug treatment, including a patient's eligibility for and the administration of rtPA
- Summarize the principles of the medical management of intracranial and subarachnoid hemorrhage

A BRIEF HISTORY OF STROKE TREATMENTS

Until recently, the medical arsenal contained few actual treatments for stroke. As Gerber (2003) wrote in her review of the history of stroke therapies:

The only treatment option available to stroke patients during the first half of the 20th century was rehabilitation. Rehabilitation as a treatment option was a great place to start; however the patient first had to survive the initial injury and somehow avoid all secondary injuries to even be a candidate for stroke treatment.

Between the 1960s and 1980s, the technique of endarterectomy for unblocking carotid arteries was improved and used widely, but this surgery was done as a preventative treatment rather than as a stroke therapy. Another key innovation in the medical management of stroke was the development of computed tomography (CT), which became available throughout the United States in the 1970s and 1980s. CT scanning proved an excellent imaging technique for distinguishing between ischemic and hemorrhagic strokes.
A dramatic step forward took place in 1996 when the FDA approved the use of a thrombolytic agent for stroke. For some patients, this drug—recombinant tissue plasminogen activator (rtPA)—can reverse the neurological effects of an acute ischemic stroke.

In the years when stroke treatment had revolved around rehabilitation, the watchwords for therapy were "supportive care" and "caution." Some physicians waited 12–24 hours to commit to a diagnosis of stroke, because transient ischemic attacks (TIA) and minor strokes were thought to clear autonomously within 24 hours. The introduction of thrombolytic treatment changed the cautious approach of stroke management. RtPA must be administered soon after a stroke occurs, and the new paradigm considers all stroke symptoms to be potential emergencies in the class of acute myocardial infarctions. Now, the slogan is "time lost is brain lost."

Thrombolytic treatment for the most common strokes (i.e., ischemic strokes) is time dependent. Although there has not yet been the same dramatic innovation for treatment of hemorrhagic strokes, which are less common than ischemic strokes, they too require emergency care. Hemorrhagic strokes often deteriorate rapidly, producing severe neurological deficits and a high rate of death and disability.

Current Management of Acute Strokes

Current management of all acute strokes stresses early identification and quick, efficient treatment using blood pressure control, lytic agents, surgical and catheter procedures, and anticoagulation. The new protocols require that EMS personnel, emergency department doctors and nurses, and surgical, neurological, and radiological specialists all be prepared to work on stroke victims quickly and efficiently (Chung & Caplan, 2007).

Today, there is still no effective "in-the-field" treatment for a stroke. Stroke patients must be taken to a hospital. Moreover, they must be taken quickly, because the clock is ticking for acute stroke victims: secondary damage from strokes increases as time passes, and early intervention can save critical brain tissue.

The rapid diagnosis of an acute stroke and the determination of its type allow a stroke team the widest range of direct treatment options. Thrombolytic treatment ("clot-busting") of ischemic strokes is recommended only within a limited time window (currently, 4.5 hours after the initial stroke symptoms). Time is such a critical element that a written time sheet is maintained for each stroke patient. Timekeeping is one of the important tasks for the emergency department (ED) and stroke team nurses; nurses are the team members who keep stroke care on schedule (Oliveira-Filho & Koroshetz, 2009b; Summers et al., 2009).

TWO TREATMENT PATHWAYS FOR STROKE VICTIMS

The availability of a time-dependent treatment for certain acute strokes sets a schedule in the emergency department. Patients who are eligible for treatment with rtPA benefit the most when they are treated quickly, and it has been estimated that an efficient ED should be able to identify most candidates for rtPA treatment within 45 minutes of their presentation to the hospital. Therefore, the current goal for EDs is to channel stroke victims into one of two treatment pathways in 45 minutes:

- **RtPA pathway.** Stroke patients with no bleeding and with evidence of an obstructed cerebral artery (i.e., an ischemic stroke) should be managed using a protocol that can lead to rapid intervention, typically with the IV administration of a "clot-busting" drug.
- **Other acute strokes.** Stroke patients with any sign of intracranial bleeding should be managed using a protocol that is based on close monitoring and individualized treatment of medical complications.

In other words, by 45 minutes, the stroke team should have distinguished ischemic from hemorrhagic strokes.

The Ischemic Stroke Goal

An ischemic stroke usually results in a gradient of decreased brain perfusion. The central area—the core area—that is fed by the blocked artery receives the least oxygenated blood. At the same time, the periphery of the area fed by the blocked artery can still be receiving sufficient blood flow to keep brain tissue alive; these peripheral areas are called the penumbra of the stroke.
The core of the stroke area infarcts rapidly because any brain tissue that is receiving little or no blood flow begins to die in <10 minutes. The penumbra, however, can still be receiving sufficient blood flow to keep its neurons from dying, although the reduced blood flow has stopped their ability to signal. Many of these penumbral neurons can be revived if blood flow is restored early enough.

Therefore, current treatments for ischemic stroke attempt to reperfuse the penumbral regions of the brain. The main reperfusion technique is thrombolysis, i.e., dissolving the arterial obstruction with a clot-lysing drug (Bravata et al., 2002; Arieff, 2004; Smith, 2007; White et al., 2007).

The Hemorrhagic Stroke Goal

Hemorrhagic stroke is the polar opposite. Bleeding will only worsen if thrombolytic drugs are given during a hemorrhagic stroke. Therefore, therapy for hemorrhagic strokes avoids interfering with the clotting pathways. Instead, hemorrhagic stroke treatment attempts to encourage the natural clotting processes with bed rest and the maintenance of adequate ventilation and blood volume. Concurrently, excessively elevated hypertension is gently lowered, as is increased intracranial pressure.

Another step is often added when the hemorrhage is subarachnoid, e.g., as the result of a ruptured aneurysm. In such cases, surgical or endovascular techniques are used to obliterate the aneurysmal remnant in an attempt to prevent rebleeding.

TREATING ISCHEMIC STROKE

Stroke patients with cerebral arteries that have been acutely blocked by clots can sometimes recover more quickly and more completely if treated with the fibrinolytic drug rtPA. This is a time-limited treatment:

- **3 hours post stroke.** As of end of 2009, it is **recommended** that eligible patients with an acute ischemic stroke be given IV rtPA treatment if the drug can be administered within 3 hours of the onset of clearly defined stroke symptoms.
- **4.5 hours post stroke.** If treatment can be started between 3 and 4.5 hours after the onset of symptoms, then IV rtPA is **suggested**.
- **>4.5 hours post stroke.** Generally, IV rtPA is not suggested after 4.5 hours.

Certain patients to whom IV rtPA cannot be given may be eligible instead for catheter administered intra-arterial rtPA. Other treatments for ischemic stroke are being tested, but none is yet recommended for widespread use later than 4.5 hours after the stroke symptoms appeared.

Fibrinolysis with rtPA

A variety of interventional stroke treatments are actively being pursued, but at the end of 2009, the only interventional treatment recommended for general use for acute ischemic stroke is the thrombolytic drug rtPA. For eligible stroke patients, IV rtPA can improve their outcome (Adams et al., 2007; Khaja & Grotta, 2007; Smith, 2007; White et al., 2007). If treated within 3 hours of the onset of their symptoms, 80% of eligible patients will survive at least 3 months and 38% will have a complete or nearly complete recovery (vs. 21% when treated with placebo). Of the survivors, 60% will be independent in their activities of daily living, 20% will remain moderately dependent on caregivers, and 20% will be completely dependent on others (Saver & Kalafut, 2007).

**WHAT IS rtPA?**

*TPA* is the abbreviation for **tissue plasminogen activator**, a naturally occurring human enzyme. RtPA is tPA that has been made in the lab using recombinant DNA technology.

Tissue plasminogen activator is a protease that turns plasminogen into plasmin, which is a molecule that cuts apart the fibrin strands holding blood clots together. In the circulation, rtPA has a half-life of 5–10 minutes (Majerus & Tollefsen, 2006).
The generic name for rtPA is alteplase, and the brand name is Activase. The drug is a white powder that is reconstituted in sterile water. Besides being used to treat acute ischemic stroke, rtPA is used to treat acute myocardial infarction.

(A brief video reviewing the action of alteplase can be viewed on the Activase website. This video is produced by the maker of Activase, but it is scientifically accurate and unbiased.)

ELIGIBILITY FOR rtPA

To use rtPA safely and effectively, the patient must have an acute ischemic stroke, not a hemorrhagic stroke. Eligible patients cannot be at risk for significant bleeds: they cannot have had recent major surgery, myocardial infarction, stroke, or other internal injuries; and they must have normal clotting functions and a sufficient number of platelets. Additionally, the patient cannot have significant hypertension (Oliveira-Filho & Koroshetz, 2009a). (See "Conditions under Which a Patient Is Eligible for rtPA" below.)

Beyond the patient's characteristics, eligibility depends on the time window. The results of using the drug are best when it has been administered within 90 minutes of the onset of stroke symptoms. The value of using rtPA is reduced but beneficial within 180 minutes, and the benefits still outweigh the risks at 270 minutes. By 360 minutes after symptom onset, however, the potential benefits of rtPA treatment no longer outweigh the risk of inducing intracerebral hemorrhage (del Zoppo et al., 2009).

CONDITIONS UNDER WHICH A PATIENT IS ELIGIBLE FOR rtPA

**Stroke status:**

- The patient has a diagnosis of ischemic stroke causing measurable neurological deficits
- The neurological signs are not clearing spontaneously
- The neurological signs are not minor and isolated
- The symptoms of stroke are not suggestive of subarachnoid hemorrhage
- The treatment can be started <4.5 hours after the onset of symptoms*
- There has not been a seizure with postictal residual neurological impairments**
- CT does not show a multilobar infarction (hypodensity >1/3 cerebral hemisphere)
- The blood glucose concentration is >50 mg/dl (2.7 mmol/L)
- Special caution will be exercised in treating a patient with major deficits (i.e., NIHSS score >22)

**Blood vessel status:**

- No head trauma or prior stroke in the previous 12 weeks
- No myocardial infarction in the previous 12 weeks
- No gastrointestinal or urinary tract hemorrhage in the previous 3 weeks
- No major surgery in the previous two weeks
- No arterial puncture at a noncompressible site in the previous 1 week
- No history of previous intracranial hemorrhage
- Blood pressure is not too high—specifically, systolic pressure is <185 mm Hg and diastolic pressure is <110 mm Hg***
- No evidence of active bleeding or acute trauma (e.g., a fracture) on examination

**Thrombotic status:**
- Not taking an oral anticoagulant, or
  - If anticoagulant is being taken, INR (international normalized ratio) <1.7
  - If patient received heparin in previous 48 hours, their aPTT (activated partial thromboplastin time) must be in a normal range
- Platelet count >100,000 mm$^3$

**Understanding risks/benefits**

- The patient or family understands the potential risks and benefits of treatment

* The currently available research demonstrating the value of using rtPA between 3 and 4.5 hours after the onset of stroke symptoms is from a study with a more limited set of patients than the study of rtPA administration <3 hours after stroke onset. The study at the later time period only followed patients <80 years, with an NIHSS>25, without the combination of previous stroke and diabetes, and not taking anticoagulants, regardless of their current INR value (del Zoppo et al., 2009).

** A patient with a seizure at the time of onset of the stroke might still be eligible for treatment provided the clinician is convinced that the residual impairments are due to a stroke and not to the seizure.

*** If greater than these levels, the patient can be given 1 or 2 doses of labetalol or a similar drug and then treated if the blood pressure decreases to the indicated range, providing that the other eligibility criteria are met.

Source: Quoted from Oliveira-Filho & Koroshetz, 2009a, which is a reorganization of Adams et al., 2007.

**ADMINISTRATION of rtPA**

The protocol for administering rtPA should be written, and it should be reviewed in advance by the involved members of the stroke team.

**Before Giving rtPA**

Treating an ischemic stroke with rtPA must be done promptly. Therefore, stroke EDs need in-place orders for the drug and a pre-arranged procedure for getting the drug from the pharmacy quickly at any hour (Lutsep & Clark, 2007).

When possible, informed consent is obtained from the patient or from a surrogate. Verbal consent is adequate. RtPA is an FDA-approved treatment for acute stroke, and if appropriate consent cannot be obtained, the drug can still be administered in an emergency (Oliveira-Filho & Samuels, 2009).

**INFORMED CONSENT FOR rtPA ADMINISTRATION**

Following is a suggested text for informing rtPA patients of the risks and benefits of rtPA:

There is a treatment for your stroke called alteplase that must be given within 4.5 hours after the stroke started. It is a "clot-buster" drug. Overall, it is estimated that alteplase treatment is 10 times more likely to help than to harm eligible patients when given within 3 hours of stroke onset. The likelihood of benefit decreases with time, but treatment is still more likely to help than harm up to 4.5 hours after the stroke begins. Thus, the potential benefits of this treatment...
However, this treatment has a major risk, since it can cause severe bleeding in the brain in about 1 of every 15 patients. If bleeding occurs in the brain, it can be fatal. When used to treat large numbers of stroke patients, on average the potential benefits of this treatment outweigh the risks; however, in any individual patient it is a very personal decision. (Oliveira-Filho & Samuels, 2009)

AN ADDITIONAL LEGAL NOTE

Malpractice suits have been brought for failure to offer or to administer rtPA to eligible patients (Saver & Kalafut, 2007). When it is consistent with the best clinical practice, thrombolytic therapy can be administered even if the patient is unable to authorize it and when a legally authorized representative is not available (Oliveira-Filho & Samuels, 2009). However, the "best clinical practice" has not yet been firmly established across the United States. The FDA guidelines are not precise, and the American Heart Association/American Stroke Association recommendations emphasize that neurologists must use their own clinical judgment. Therefore, as a legal safeguard, doctors should discuss treatment options (including getting a second opinion and transferring the patient to another institution) with patients and family when there is sufficient time. Doctors should then document the discussions or the need for immediate treatment without these discussions (Weintraub, 2006).

Before giving the drug, all procedures that might induce bleeding, such as inserting Foley catheters or nasogastric tubes, should be completed. At least two large bore IV lines must be in place.

Usually, a nurse administers rtPA. The nurse begins by rechecking the eligibility of the patient, including the verification of adequate coagulation functions, sufficient platelets, a head scan showing no hemorrhage, and that time remains in the 4.5-hour window after the onset of stroke symptoms.

While Giving rtPA

rtPA is given intravenously. The total dose is 0.9 mg/kg up to a maximum of 90 mg (i.e., all patients weighing >100 kg (220 lb) receive a total of 90 mg of drug). If all of the drug in the bottle will not be needed, the excess is removed in advance and discarded to prevent accidental overdose. The first 10% of the dose is given as a bolus, and the remainder is delivered as a 60-minute infusion (Saver & Kalafut, 2007; Oliveira-Filho & Samuels, 2009). Verifying doses, infusion settings, and the amount of any discard with a second nurse is key to avoiding errors (Summers et al., 2009).

During the infusion and in the succeeding 24 hours, acute hypertension, severe headache, nausea, or vomiting can be signs of intracranial bleeding. If any of these arise, the infusion must be stopped and an emergency CT obtained. Immediate blood work is also done to check the patient's platelet count and coagulation functions. In addition, emergency neurosurgical and hematologic consults are called to advise on the immediate treatment plan (Saver & Kalafut, 2007).

In the hands of experienced neurologists following recommended guidelines, symptomatic intracerebral hemorrhages will be caused in about 6% of rtPA treatments. No characteristics of the patients or their strokes have yet been found that can reliably predict who will suffer a symptomatic intracerebral hemorrhage when treated with rtPA (Caplan, 2009; Oliveira-Filho & Samuels, 2009).

After Giving rtPA
After giving the drug, the patient must be monitored closely in an intensive care unit for at least 24 hours. Vital signs are checked every 15 minutes for 2 hours, every 30 minutes for the next 6 hours, and once every hour for the following 16 hours. A neurological assessment is done each time the vital signs are taken.

During the first 24 hours, blood pressure is maintained at <180/105 mm Hg, no antiplatelet or anticoagulant drugs are given, and no arterial punctures are done. Likewise, intra-arterial catheters, nasogastric tubes, and indwelling bladder catheters are not inserted during the first 24 hours.

Even in the best of circumstances, however, almost 1/3 of patients will develop oozing from around IV lines and at venous puncture sites after rtPA treatment; gum bleeding and ecchymoses (e.g., under automated blood pressure cuffs) are also common. On rare occasions, internal bleeding and even cardiac tamponade can result from rtPA administration, so hypotension must be investigated immediately using ultrasound (Oliveira-Filho & Samuels, 2009).

**Intra-arterial Fibrinolysis with rtPA**

Normally, rtPA is given intravenously. A higher concentration can be delivered to the clot by injecting rtPA through an intra-arterial catheter placed near the clot. Intra-arterial thrombolysis has been used to treat large clots in the middle cerebral artery, life-threatening basilar artery clots, and in certain other cases when patients are not eligible for IV rtPA. When administered intra-arterially, the total dose of rtPA is about 1/3 of that used intravenously. Ongoing studies are also testing the efficacy of combining intravenous and intra-arterial thrombolysis in serious strokes (Oliveira-Filho & Samuels, 2009; Gounis et al., 2010).

**Treatment with Other Anti-thrombotic Drugs**

Many acute stroke victims are not eligible for rtPA therapy. In some of these patients, other anti-thrombotic drugs have been tried acutely. Currently, aspirin is the only antiplatelet drug recommended for treating some acute ischemic stroke patients. Studies show that when begun within 48 hours of the onset of stroke symptoms, aspirin (160–300 mg/day) reduces the incidence of stroke recurrence, improves overall outcome compared to no treatment, and may reduce mortality by about 1% (Oliveira-Filho & Koroshetz, 2009).

**RECOMMENDED ASPIRIN THERAPY**

| For acute ischemic stroke patients who are not receiving rtPA, IV heparin, or oral anticoagulants, daily aspirin (325 mg on the first day followed by 150–325 mg/day thereafter) is recommended, beginning within the first 48 hours. Aspirin is not a substitute for other stroke treatments. |

Studies of anticoagulation with heparin or low molecular weight heparin have not demonstrated benefits for most acute ischemic stroke patients. Anticoagulation cannot be used in patients with hemorrhagic stroke; and stroke patients with large infarctions, uncontrolled hypertension, or bleeding conditions should not be given full-dose anticoagulation treatment. On the other hand, neurologists sometimes use anticoagulation in selected stroke patients with:

- Cardioembolism from intracardiac thrombus that is associated with significant valvular disease, severe congestive heart failure, or mechanical heart valves
- Large artery atherosclerotic stenosis with intraluminal thrombus
- Dissection of a cervical or intracranial large artery
  
  (Oliveira-Filho & Koroshetz, 2009)

**Endovascular Devices**

Researchers are also exploring the use of mechanical devices to physically open cerebral artery blockages. These devices range from clot removers or retrievers to angioplasty catheters to deployers of self-expanding
One goal of the development of physical clot disruption devices is to provide acute stroke treatments that can be used when thrombolytic drugs would endanger the patient, such as after recent cardiac surgery. Although they can be used alone, physical clot disruption techniques are typically used along with catheters delivering intra-arterial rtPA. Many endovascular devices show promise; none is yet recommended for widespread community hospital use (Oliveira-Filho & Samuels, 2009; Gounis et al., 2010).

Treatig Concurrent Hypertension

Acute ischemic strokes usually present with elevated blood pressure, but this is not always an indication for aggressive treatment of the hypertension. After a stroke, some degree of hypertension may be needed to maintain adequate perfusion of the brain, although very high blood pressure (systolic pressure >200 mm Hg) has been linked to higher mortality rates after stroke.

Currently, it is recommended that mild or moderate hypertension not be initially treated in an acute ischemic stroke. With this general rule comes a list of situations in which hypertension should usually be reduced:

- Extreme hypertension, i.e., systolic pressure >220 mm Hg or diastolic pressure >120 mm Hg
- Active coronary artery disease
- Heart failure
- Aortic dissection
- Hypertensive encephalopathy
- Acute renal failure
- Pre-eclampsia or eclampsia

When lowering blood pressure in an acute ischemic stroke, IV labetalol is commonly used, and the goal is a cautious reduction in blood pressure of about 15% during the first 24 hours.

A different blood pressure goal is used for patients who are eligible for treatment with rtPA:

- Before administering rtPA, patients should be treated to reduce their systolic blood pressure to ≤185 mm Hg and their diastolic blood pressure to ≤110 mm Hg.
- After rtPA therapy, patients' blood pressure should be maintained at <180/105 mm Hg for at least 24 hours (Oliveira-Filho & Koroshetz, 2009a, c).

TREATING HEMORRHAGIC STROKE

The treatment paths for a stroke victim diverge dramatically at the point in the stroke evaluation where the physician answers the question, "Are there any signs of intracranial hemorrhage?" Strokes with bleeding cannot be treated using fibrinolytic drugs because these drugs will make the patient's condition worse. Head imaging is the best way to identify intracranial hemorrhaging, and CT or MRI studies must be done early in a patient's evaluation so that subsequent treatment can be started quickly.

For intracerebral hemorrhages (ICH), treatments attempt to stop or decrease the bleeding, remove extravascular blood, and maintain the patient in a well-oxygenated nonhypertensive state; the specific treatment steps are decided on a case-by-case basis. For subarachnoid hemorrhages, the goals are similar, the treatments are also individually tailored, and there is the additional possibility of physically stabilizing ruptured aneurysms.

As treatment plans are formulated for a patient with an intracranial hemorrhage, it is important to check the patient's current medications. Existing anticoagulation, such as warfarin therapy, is a common cause of cerebral bleeds. In such patients, the anticoagulant drug must be stopped and its effects reversed. Usually, this requires IV vitamin K, prothrombin-complex concentrates, fresh frozen plasma, or recombinant human clotting factor VIIa (Oliveira-Filho & Koroshetz, 2009b).

Intracerebral Hemorrhages

Approximately 10% of all strokes are intracerebral hemorrhages (ICH), i.e., bleeds into the substance of the
brain. ICH has a high mortality rate (35%–52% within the first month), and most of the deaths occur within the first 48 hours (Rordorf & MacDonald, 2009). Larger hemorrhages have poorer prognoses, especially when the stroke has led to coma (Steiner & Bosel, 2010).

**BASIC MEDICAL MANAGEMENT**

Currently, basic medical management appears to be more beneficial than any surgical interventions for most ICH. Patient treatment must be individualized, but some general goals include addressing the following concerns:

**Bed rest.** The patient needs constant hemodynamic monitoring in an ICU.

**Ventilation.** Adequate ventilation and oxygenation should be ensured.

**Fever.** For any increase in body temperature, antipyretic medicines are administered to lower the body temperature to normal.

**Hyperglycemia.** Insulin is used to lower blood glucose levels to <140 mg/dl.

**Hydration.** Hypovolemia should be corrected using IV normal saline.

**Increased intracranial pressure (ICP).** If increased ICP is suspected, the head of the bed should be elevated to 20°–30°. Analgesia (morphine or alfentanil) and sedation (propofol, etomidate, or midazolam) can often help to reduce ICP. Dehydrating agents such as mannitol are sometimes administered with the goal of making the blood plasma hyperosmolar (300 to 310 mOsm/L). Treatments for increased ICP are best monitored by continuous direct measurement of the ICP. (See "Acute Complications" below for more details.)

**Hypertension.** Most patients with an intracerebral hemorrhage are hypertensive immediately after the stroke, and some degree of hypertension may be necessary to maintain sufficient perfusion throughout the brain. However, severe hypertension can worsen the stroke, so high blood pressure is usually treated with an IV antihypertensive (e.g., labetalol).

Treatment recommendations for hypertension in acute ICH are:

- For SBP >200 mm Hg or MAP >150 mm Hg
  - Administer an IV antihypertensive drug, monitor BP every 5 minutes
- For SBP >180 mm Hg or MAP >130 mm Hg
  - When ICP is elevated, administer an IV antihypertensive drug to maintain CPP between 61 mm Hg and 80 mm Hg
  - When ICP is normal, administer an IV antihypertensive drug to maintain BP ~160/90 mm Hg or MAP ~110 mm Hg

(SBP=systolic BP; MAP=mean arterial BP; ICP=intracranial pressure; CPP=cerebral perfusion pressure, which can be calculated as CPP=MAP–ICP)

**OTHER INTERVENTIONS**

**Infusion of hemostatic agents.** Studies are ongoing, but the prothrombotic agents tested to date have not proved beneficial.

**Surgical evacuation of hematoma.** In general, surgical interventions have given no better results than medical management. Surgery can be critical, however, for reversing brainstem compression or for relieving hydrocephalus (e.g., from an expanding cerebellar hemorrhage) (Ropper & Samuels, 2009a; Rordorf & MacDonald, 2009).

**DO NOT RESUSCITATE (DNR) ORDERS AND INTRACEREBRAL HEMORRHAGE (ICH)**
Existing DNR orders must be respected. However, DNR orders newly assigned in the hospital early in the treatment of acute ICH have been shown to operate as an unstated commitment to nonaggressive therapy.

During the first 24 hours, physicians are sometimes overly pessimistic about the prognosis for ICH patients. "Early DNR orders or limitations to care are not always inappropriate after ICH; the difficulty lies in deciding when such limitations are indeed the most appropriate approach. Current guidelines suggest careful consideration of aggressive full care during the first 24 hours after ICH onset and postponement of new DNR orders during that time. The recommendation does not apply to patients with preexisting DNR orders" (Rordorf & MacDonald, 2009).

Subarachnoid Hemorrhages

Approximately 3% of all strokes are subarachnoid hemorrhages (SAH), most of which result from ruptured aneurysms. Like ICH, SAH has a high mortality rate; for SAH, mortality is almost 50% within the first month. Large hemorrhages and hemorrhages producing coma or stupor have the poorest prognoses (Singer et al., 2009).

BASIC MEDICAL MANAGEMENT

Currently, medical management is the basis of treatment for SAH, with percutaneous or surgical obliteration of the remnants of the aneurysm when possible (Ropper & Samuels, 2009b). Patient treatment must be individualized, but some general goals include addressing the following concerns:

Bed rest. Patients have constant hemodynamic monitoring in an ICU. A set of baseline Transcranial Doppler (TCD) ultrasonography measurements is taken; repeat TCDs are then used to monitor for vasospasms, especially in the middle cerebral and basilar arteries. Prophylaxis is instituted against deep venous thrombosis by applying pneumatic compression stockings.

Ventilation. Adequate ventilation and oxygenation should be ensured.

Fever. For any increase in body temperature, antipyretic medicines are administered to lower the body temperature to normal.

Hyperglycemia. Insulin is used to lower blood glucose levels to <140 mg/dl.

Hydration. In the majority of patients, intravascular volume becomes depleted in the days after a subarachnoid hemorrhage, and this greatly increases the chances of an ischemic infarction from vasospasm. Therefore, fluids are given to maintain an above-normal circulating blood volume and central venous pressure.

pH. Metabolic acidosis is a complication to watch for and correct.

Pain. Analgesia is given for headache.

Increased intracranial pressure (ICP). Intracranial pressure can increase, so when possible, some centers place a ventriculostomy to directly monitor ICP.

Hypertension. Some degree of hypertension may be needed to maintain sufficient perfusion throughout the brain. If ICP measurements are available, they can be used to calculate the cerebral perfusion pressure (CPP) using the mean arterial pressure (MAP), because CPP=MAP–ICP. Therefore, when ICP values are known, blood pressure can be titrated to maintain the CPP between 61 mm Hg and 80 mm Hg. When ICP measurements are not known, the systolic blood pressure in conscious patients can usually be reduced to <140 mm Hg. In patients with impaired consciousness, hypertension is usually not treated. Labetalol is the commonly used antihypertensive drug.

Prevention of stroke from vasospasm. Repeat TCD measurements are used to monitor for vasospasm. Small
studies suggest that by initiating statin treatment within 48 hours of an aneurysmal SAH or by continuing a preexisting statin, the incidence of vasospasms and the subsequent mortality rates are reduced.

OTHER INTERVENTIONS

Infusion of hemostatic or antifibrinolytic agents. Studies are ongoing, but the prothrombotic agents tested to date have not proved beneficial.

Nimodipine therapy. By an unknown mechanism, nimodipine (a calcium channel blocker) improves the outcome of patients with an acute SAH. The standard therapy is the administration of nimodipine 60 mg PO every 4 hours, beginning within 96 hours of the stroke's onset. When giving nimodipine, the patient must be monitored for hypotension.

Surgical and percutaneous obliteration of the aneurysm. The risk of rerupture of an aneurysm and some of the secondary problems that arise because of blood in the subarachnoid space can be reduced by early obliteration of the aneurysm. Surgically, aneurysms are occluded with external clips, typically made of titanium. Percutaneously, some aneurysms can be occluded by injecting them with a platinum coil; the coil then becomes coated with thrombus, which fills (and obliterates) the space in the aneurysmal sac (Ferris et al., 2009; Ropper & Samuels, 2009b; Singer et al., 2009).

TIME-DEPENDENT STROKE TREATMENT BY REMOTE CONSULTATION

The time-dependent stroke treatments, such as intravenous rtPA, are only recommended for use in hospitals with experienced staff and well-equipped facilities. Ideally, the treatment of all acute strokes would be done in primary stroke centers, but many areas of the country are far from primary stroke centers. One way to extend the range of acute stroke treatment, especially the administration of thrombolytic agents, into areas far from stroke specialists is by using video teleconsultation or "telestroke."

Telestroke is a two-way videoconference between distant stroke-care specialists and local bedside-care physicians. Telestroke works exactly like a direct onsite consultation, and as with onsite consultations, patients or their families are kept involved and asked to grant permission. Telestroke is not considered therapy: it is a consultation to advise the local physicians who are doing the therapy. At the moment, medical licensing liability laws may limit the use of out-of-state telestroke consultations.

Telestroke, which is endorsed by the American Heart Association (Schwamm et al., 2009), has proved effective and cost-efficient. The following telestroke case history was reported by a group of neurologists at the primary stroke center of the Medical College of Georgia (Hess et al., 2006). It is a good example of how telestroke can extend time-dependent stroke therapy into communities far from primary stroke centers.

CASE HISTORY

A 62-year-old woman with a history of paroxysmal atrial fibrillation suddenly develops weakness of her left arm and left leg and falls when getting out of her car on her way to an exercise class. During the fall, she sustains trauma to her left orbit. She is taken to the local 56-bed rural hospital in Washington, Georgia, and arrives in the emergency department within 30 minutes. The emergency room physician activates a REACH (remote evaluation of acute ischemic stroke) telestroke consultation with the Medical College of Georgia, 61 miles away in Augusta, Georgia.

During examination over remote video, the patient shows severe neglect and a dense left hemiparesis. Her National Institute of Health Stroke Score (NIHSS) is 16. She has swelling over the left eye, making it difficult for her to open her eyelid. The CT scan of brain—viewed remotely by a personal access communications system built into REACH—is normal without any evidence of hemorrhage or early infarct signs. The consultant advises alteplase, and the REACH system calculates a weight-based dose. Recommendations, including dose of alteplase, are printed out at the local rural hospital. Ninety mg of alteplase is started intravenously at 1 hour and 50 minutes from the time of symptom onset. The patient is transferred by helicopter to the Medical College of Georgia.
NEUROPROTECTION, A FUTURE TREATMENT

Neuroprotective techniques are attempts to slow the degeneration of injured brain cells until sufficient arterial perfusion can be reestablished. Still experimental, the neuroprotective ideas include:

- **Neural transmission blockers.** One result of ischemia is the depolarization of nerve cells, which causes a destructive release of excitatory neurotransmitters. These neurotransmitters speed the depletion of energy stores and flood the local environment with depolarizing ions. Drugs that selectively block excitatory neurons are being tested as neuroprotective agents after stroke injury (Lutsep & Clark, 2006).

- **Hypothermia.** In some hypothermic situations (e.g., after having been buried in an avalanche), patients have successfully been revived after their brains had suffered >2 hours of oxygen deprivation (Oechmichen & Meissner, 2006). Animal studies have shown that it may be possible to produce a controlled hypothermia that can act as a temporary neuroprotectant after an acute stroke.

- **Free radical scavengers.** Elevated levels of reactive free radicals in ischemic tissue hasten the cellular damage. Therefore, free radical scavengers have been explored as agents that can slow the degeneration of brain tissue in acute ischemic stroke (Oliveira-Filho & Koroshetz, 2009a).

SUMMARY

In the last fifteen years, the use of recombinant tissue plasminogen activator (rtPA) to fragment clots has revolutionized the treatment of acute strokes. Eighty percent more of the eligible patients have a complete or nearly complete recovery from an ischemic stroke when treated with rtPA compared to being untreated, as was previously the case.

With rtPA in the doctors' arsenal, treatment paths differ for strokes with and without bleeding. In the ED, the critical step is distinguishing between ischemic and hemorrhagic strokes. For ischemic strokes, IV recombinant tissue plasminogen activator (rtPA) should be administered to eligible patients within 4.5 hours of the onset of symptoms. To be eligible, patients must not be pregnant, must have a sufficiently high platelet count, and can have no indication of intracranial hemorrhage, no recent major surgery, no evidence of internal bleeding, no known bleeding diatheses, and no current anticoagulant therapy. After receiving IV rtPA, patients must be carefully monitored for at least 24 hours in an ICU.

For those hemorrhagic strokes that are due to a ruptured subarachnoid aneurysm, neurosurgery is consulted for possible treatment by surgically clipping the aneurysm remnant or by endovascularly inserting a coil. For other subarachnoid hemorrhages, for intracerebral hemorrhages, and for ischemic strokes ineligible for rtPA treatment, patients are admitted directly to an ICU and are monitored carefully.

RESOURCES

American Stroke Association (A Division of American Heart Association)
http://www.strokeassociation.org
REFERENCES


