

# The Five Ps of Acute Ischemic Stroke Treatment: Parenchyma, Pipes, Perfusion, Penumbra, and Prevention of Complications

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**Stroke is a treatable disease. Despite the therapeutic nihilism of the past, the advent of thrombolysis has changed the way stroke treatment is approached. Acute ischemic stroke is a challenging and heterogeneous disease, and treatment must be based on an understanding of the underlying pathophysiology of ischemia. Interventions are designed to improve neuronal salvage and outcome. The underlying tenets of stroke therapy focus on the brain parenchyma, arterial flow (pipes), perfusion, the ischemic milieu or penumbra, and prevention of complications. This article focuses on the practical issues of ischemic stroke care with a brief review of supporting literature.**

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Stroke therapy and care are advancing at a welcome pace. However, despite FDA-approved therapies and national educational efforts, 97% of acute stroke victims nationwide are not being offered thrombolysis. In addition, many non-proven and potentially harmful therapies remain in common usage. The lack of standardization in stroke care may be due to the complicated and heterogeneous nature of ischemic stroke.

Howard A. Rowley has put forth the "4 Ps" concept of acute ischemic stroke imaging (1). We borrow from this simple concept to clarify our approach to acute stroke treatment and hope to assist clinicians in understanding the underlying evidence and pathophysiology of basic stroke care.

## **PARENCHYMA**

Stroke is caused by ischemia to the neuronal structures. Although nearly 85% of strokes are ischemic in nature, there are multiple subtypes of ischemic strokes with differing presentations, etiologies, prognoses, and treatments. The remaining 15% of strokes are hemorrhagic in nature with aneurysmal rupture and subarachnoid hemorrhage comprising 5%-6% of all strokes. Intracerebral hemorrhage makes up the remaining 10%. The damage from

intracerebral hemorrhage appears to occur in the first moments after stroke, and treatment is mainly supportive (2). Ischemic stroke is the emphasis of this article.

Ischemic stroke generally presents with a sudden and painless loss of neuronal function typically occurring due to thrombotic occlusion of a supplying artery. When neuronal tissue, which normally receives 60 mL to 70 mL of perfusion per 100 g of brain tissue per minute, has a reduction of flow to 25 mL/100 g/min, aerobic metabolism cannot be maintained and loss of function occurs. Prolonged ischemia results in a stereotypical series of biochemical events leading to eventual cell death, the so-called "ischemic cascade" (3).

The first task in stroke treatment is differentiating ischemic from hemorrhagic stroke. Hemorrhagic stroke cannot be excluded based on clinical examination and history. Prior to any intervention, a CT image of the brain is mandated to differentiate ischemic from hemorrhagic stroke. MRI is also being investigated for this purpose (4).

The importance of early CT findings of acute ischemic stroke is controversial, mainly due to lack of intra-observer agreement. When presented with definite clinical scenarios and direct questions

on the size and nature of a CT abnormality, general neurologists and radiologists are not perfect (5) and even experts have fair agreement at best (6). Treating clinicians should have an appreciation of neuroimaging, and a close relationship with radiology is a requirement.

### The Stroke Syndromes

There are three general ischemic stroke syndromes (Table 1). The first of these syndromes is the lacunar strokes, which are due to ischemia within the deep arterioles supplying white matter structures and the thalamus. Caused by a process of intimal reduplication or lipohyalinosis, these strokes typically have the best prognosis. Since they are caused by the compromise of small vessels, angiography studies are often normal. However, despite the lack of visualized thrombus, these strokes do respond to systemic thrombolysis.

The second typical stroke syndrome is due to thrombotic occlusion of the major intracranial vessels. These produce large, wedge-shaped, cortical infarctions and present with a loss of the eloquent functions such as language. This stroke subtype is the best studied but often has a poor prognosis, as with the so-called malignant middle cerebral artery syndrome (7). The etiology is nearly always embolic, either from unstable plaque (atheroemboli), cardiac sources (cardioembolism), or spontaneous thrombosis due to hypercoagulable states. A thrombus can be visualized 80% of the time during angiography.

The third stroke subtype is brainstem stroke. Although brainstem stroke may be caused by either small vessel (pontine perforating) or large (basilar artery) vessel compromise, clinical presentation can be confusing. Brainstem ischemia can present with variable cranial neuropathy, hemiparesis, and levels of consciousness. It is also important to remember that posterior circulation terminates in posterior cerebral arteries, and occipital infarcts with resultant visual field deficits are common. Reference to a textbook on neurological localization is recommended for further information.

Clinically, it is not always possible to differentiate lacunar, large vessel, and brainstem infarctions. Localization and stroke subtypes point towards a causative entity and the location of arterial obstruction. This information can assist with intervention and secondary prevention.

After ensuring that there is no evidence of hemorrhage on CT imaging, the treating clinician should develop a general diagnosis for location, stroke subtype, and possible etiologies. These first steps will help determine therapy and potential intervention.

**Table 1. Anterior and posterior vascular syndromes.**  
Note: the dominant hemisphere is the side that controls language function.

#### Anterior (Carotid) Artery Syndromes

##### Middle Cerebral Artery

- Expressive aphasia: dominant posterior frontal lobe
- Receptive aphasia: dominant superior temporal lobe
- Weakness of arm ± leg: contralateral (to weakness) parietal lobe
- Loss of lateral visual fields: contralateral parietal lobe

##### Anterior Cerebral Artery

- Weakness of leg: medial (parafalcine) parietal lobe

#### Posterior (Vertebrobasilar) Artery Syndromes

- Vertigo, nystagmus that changes with the direction of gaze, cranial nerve palsies, retropulsion: cerebellum
- Hemiparesis, hemisensory loss of one half of the body, swallowing difficulty: brainstem

#### Lacunar Syndromes

(Note: these do not have the “cortical signs” of aphasia, visual loss, etc.)

- Pure motor stroke: corona radiata, internal capsule, basis pons
- Pure sensory stroke: thalamus
- Ataxic-hemiparesis, clumsy hand-dysarthria: pons
- Mixed motor-sensory stroke: junction of thalamus and internal capsule

**Table 2. Patient criteria for intravenous thrombolysis therapy with tissue plasminogen activator.**

#### Eligibility

- Clinical diagnosis of stroke causing measurable deficit
- Time of onset within 180 minutes of initiating therapy

#### Contraindications

- Evidence of hemorrhage on CT
- Clinical presentation with subarachnoid hemolysate
- Active internal bleeding
- Known bleeding diathesis
- Within 3 months of intracranial surgery, traumatic brain injury, or stroke
- History of intracranial hemorrhage, arterio-venous malformation, or aneurysm
- Uncontrollable hypertension

#### Warnings

- Minor or rapidly improving symptoms
- Gastrointestinal or urinary hemorrhage within 121 days
- Major surgery or trauma within 14 days
- Recent lumbar puncture or arterial puncture at noncompressible site
- Hyper- or hypoglycemia
- Seizure at onset of stroke symptoms
- Post-myocardial infarction pericarditis

## PIPES

Ischemic stroke is due to the compromise of flow through either large or small arteries supplying the brain parenchyma. Dissolution of this thrombus and restoration of flow is the end goal of thrombolysis. The National Institutes of Neurological Disorders and Stroke (NINDS) intravenous tissue plasminogen activator (IV-tPA) trial established the utility of intravenous thrombolysis in 1995 (8). This was the first and (thus far) only trial to show a benefit in neurologic function with treatment for stroke in a double blind, controlled, clinical trial, leading to FDA approval of an acute stroke therapy. Attempts to extend the narrow window of 3 hours from the onset of symptoms have not been successful (9). Intravenous thrombolysis continues to be the most widely accepted standard of care for patients who meet the stringent criteria (Table 2).

Some centers use intra-arterial (IA) thrombolysis for patients who do not meet the strict criteria for intravenous thrombolytic therapy. This was supported by the Prolapse in Acute Cerebral Thrombosis (PROACT) trial, which showed a significant benefit for IA therapy with pro-urokinase within a 6-hour window from the onset of symptoms (10). Many centers are using t-PA instead of pro-urokinase (11), although it has not been tested in the same rigorous fashion as urokinase for this indication. The indications for IA therapy and interventional neurology are expanding rapidly but are limited by the need for a skilled team that must be immediately available, specialized interventional physicians, and costly equipment.

Most neurointerventional therapy is centered on occlusion of the middle cerebral, or basilar artery (MCA). Much like coronary procedures, intervention may be immediate, delayed, or done as a rescue if other therapies fail. For select patients, the results are often excellent (12). In one uncontrolled series, angioplasty of proximal MCA occlusion led to a greater immediate reduction on the National Institutes of Health Stroke Scale (NIHSS), although the scores were not different the day after the intervention or a month later (12).

Angiography itself is not risk-free, and a diagnostic angiogram can cause an embolic event. In a variety of studies, the risk of stroke during a diagnostic (nonemergent) angiogram is about 1% (13,14), with permanent deficits occurring at about half that rate. The risk is substantially higher in patients with recent cerebral ischemia or stroke in progress, when there is already unstable plaque.

Intracranial techniques have changed over time allowing for the learning curve of the technique (e.g. how to size the balloon, how fast to inflate, how long to maintain inflation) and the advent of new equipment. One center has found that slightly undersizing the balloon and using slow inflation has minimized complications over a period of years (15). Rapid improvements in technique are likely to continue (16), though selection of patients remains very important. A reasonable group is patients who continue to have events on "maximal" medical therapy (however it is individually defined), and in small series, excellent results may be obtained (17).

## Medical Therapies

Fibrinolytic snake venoms show promise. The best studied is ancrod, which is derived from the Malaysian pit viper. The mechanism of action is the degradation of fibrin without platelet activation. One trial of 500 patients reached statistical significance for improved outcome when ancrod was started within 3 hours of symptom onset (18). Larger trials in Europe and China are planned. For now, ancrod is not licensed for use in the US. It is uncertain how ancrod will compare to the use of intravenous tPA, and patient selection for the competing therapies remains to be seen.

### Aspirin

Aspirin is the most commonly used antiplatelet medication. It exerts an antiplatelet effect by irreversibly acetylating and deactivating cyclo-oxygenase, halting production of thromboxane A<sub>2</sub>. A single 100 mg dose is adequate to irreversibly inhibit this mechanism of platelet activation, and the effect persists for the life of the platelets. However, it does not inhibit platelet aggregation directly.

The large Chinese Acute Stroke Trial (CAST) assessed (only) low-dose aspirin versus placebo in acute ischemic stroke (19) and found a benefit similar to the International Stroke Trial (IST, 20). When the IST and CAST are taken together, low-dose aspirin improved outcomes in about 13 per 1000 patients treated.

### Heparin

Purified from beef lung, heparin is a variety of sugar moieties with anticoagulant properties. Probably the most important mechanism of action is its potentiation of antithrombin, which decreases the activity of factors IX, X, XI, XII, and II (thrombin). It also has some modest antiplatelet effect from its inhibition of thrombin-mediated platelet aggregation. While its anticoagulant effects occur immediately upon administration, after an infusion is discontinued the half-life is approximately 1.5 hours. The other major risk of heparin is an induced thrombocytopenia (HIT). HIT occurs approximately 4-7 days after an infusion has started and is defined by a drop in platelet count of 50% or more; the only treatment is stopping the heparin. After an episode of HIT, both unfractionated and low-molecular-weight heparin have a low risk of causing HIT again. In heparin-naïve patients, low-molecular-weight heparin does not lead to HIT.

The efficacy of heparin is standardized per unit, but individual patient responses vary widely requiring intensive monitoring for patients receiving the full intravenous dose. The activated partial thromboplastin time (PTT) is the standard on hospital inpatient wards and intensive care units. While it is inexpensive and the technique is standard at higher intensities of anticoagulation, it is increasingly less accurate. The activated coagulation time (ACT) retains a linear relationship to heparin-mediated anticoagulation, and automated ACT machines may be kept in the catheterization laboratory for monitoring during procedures. Low ACT increases the risk of stent

thrombosis (21), but heparin need not be continued more than 24 hours after stent placement.

Although use of full-dose intravenous unfractionated heparin has become uncommon and generally discouraged, the use of low-dose subcutaneous heparin has acquired strong supporting evidence. The IST randomized 20,000 patients to low-dose aspirin and or low-dose heparin in a 2x2 factorial design (i.e. patients were independently randomized to receive neither, one, or both of the two treatments) (20). Although, overall, heparin in a dose of 5000 U SQ Q12 h or 12,500 U SQ Q12 h did not change outcome overall, 5000 U SQ Q12h led to significant (if modest) benefit. The group that received 5000 U SQ Q12 h and aspirin 3325 mg QD did best.

It is important to keep in mind that patient selection is very important for any stroke therapy. The relative risks and benefits of any stroke therapy must be tailored to the individual patient profile when there are not a priori defined guidelines. General considerations are outlined in Table 3.

## PERFUSION

Along with restoration, attempts to salvage the brain at risk from ischemia have often focused on increasing collateral flow. PET and SPECT imaging of stroke have demonstrated that ischemic brain parenchyma will extract the maximum oxygen; much like a miser hoards maximum available resources (22). The outlying border zones of the region of ischemia are supplied via alternate routes through the leptomeningeal collaterals from adjacent vascular territories. Increasing the quantity and quality of collateral flow to these ischemic regions provides a potential for salvage from increased nutritive perfusion.

There is strong evidence that decreased collateral flow is harmful. Due to a loss of autoregulation, brain perfusion is strongly affected by changes in systemic blood pressure. Hypotension and dehydration should be avoided. Hypertension, in the form of the Cushing response, is a normal response to cerebral ischemia. Blood pressure should not be lowered in acute stroke, except in the setting of thrombolysis or end organ damage (23). Gravitation can also affect perfusion, and patients have experienced increased deficit upon standing. Alternatively, many patients show clinical and physiological improvements with positioning the head of the bed < 30 degrees (24).

**Table 3. Patient selection for thrombolysis.**

Characteristic	Desirable/Required	Contraindicated
Intravenous thrombolysis	Start of therapy within 3h of symptom onset. Disabling deficit	Platelet count < 100 BP > 185/110 mmHg despite labetalol 20 mg IV Hemorrhage on CT Seizure at symptom onset Recent stroke, surgery, arterial puncture at noncompressible site History of intracranial hemorrhage
Intraarterial thrombolysis	Presence of catheterization team and equipment Start of therapy within 6h of symptom onset Lack of improvement with IV therapy	Inability to obtain informed consent Technical considerations

Despite some initial promise, large trials have not shown conclusive effectiveness of increasing collateral flow. Pentastarch, a synthetic albumin analogue, showed no benefit in the Hypervolemic Hemodilution Treatment of Acute Stroke trial (25). However, post hoc analysis suggested that patients who had an increase in cardiac output of >10% had improved outcomes compared with placebo and through transvenous routes have shown benefit in animal studies. Despite early encouraging results, logistical issues have hindered further trials. Summaries of intervention to maximize perfusion are shown in Table 4.

## PENUMBRA

Within minutes after an ischemic insult, a region of tissue is irreversibly damaged: the “necrotic core.” The “ischemic penumbra” surrounding the necrotic core is receiving inadequate nutritive flow and will undergo a series of preprogrammed biological steps called the ischemic cascade eventually leading to death of the cells within (3). Specific actions can be taken to minimize damage to the penumbra.

### Normoglycemia

Maintenance of normoglycemia is important beyond the general increased risk of stroke in patients with diabetes. The mechanism is believed to be related to anaerobic metabolism and increased lactic acid production; the acidosis is toxic and promotes neuronal cell death (26). Hyperglycemia itself may be due to the stress response of the event (27), but this has not been completely elucidated. The type of stroke seems to have an influence on the effects of glucose level. In the Trial of ORG 10172 in Acute Stroke Treatment (TOAST),

**Table 4.** Maximization of perfusion.

Intervention	Benefit
Induced hypertenion	Increase in cerebral perfusion pressure
Colloid solutions (hetastarch, pentastarch)	Increase in intravascular volume and tissue perfusion
Crystalloid solutions	Increase in intravascular volume
Bed positioning, bed rest	Increase in perfusion

hyperglycemia predicted worse outcome in all strokes in general, especially in nonlacunar stroke (28). Among patients treated with t-PA, absence of diabetes and normoglycemia on admission predict good outcome as well (29).

### ***Fever***

A link between neuronal damage and fever has been known for some time, but only recently has interest quickened in using hypothermia as a treatment. Fever has been reliably shown to be associated with worse outcome (30,31), and lowering body temperature may lead to neuronal salvage by a variety of mechanisms (32). Treatment of fever with antipyretic medications is standard and probably helpful. Induced hypothermia is labor intensive and costly. Cooling patients below 34°C - 35°C requires intubation, sedation, and intravenous infusion of ice-cold saline. A recent trial failed to show lower body temperatures with cooling blankets as opposed to acetaminophen alone, in part because some patients could not tolerate the blanket (33).

### ***Pharmacological Neuroprotectants***

A number of neuroprotectants have been tested in human trials after promising studies in animals, typically murine models of stroke. Despite reasonable preclinical models, dose escalation studies, and excellent clinical and statistical oversight, none of these has shown improvements in neurologic outcome. Trials of tirilizad (an inhibitor of lipid peroxidation) (34), clomethiazole (a GABA activator) (35), and lubeluzole (which inhibits an increase in extracellular glutamate) (36), among other agents, have shown no benefit.

### ***Hyperbaric Therapy***

Hyperbaric oxygen seems a logical and attractive option, but it has been difficult to show benefit despite some encouraging case reports. One pilot trial of hyperbaric oxygen therapy in acute stroke was stopped because there were difficulties in nearly all aspects: it was difficult to organize smoothly, a substantial number of patients requested the treatments be stopped, and there were worrisome trends towards harm in the oxygen group (37). This therapy is also limited by the availability of the hyperbaric chamber.

## **PREVENTING COMPLICATIONS**

Most stroke complications can be avoided. Through the use of standardized stroke pathways, nursing education, and the designation of a stroke unit, the common causes of increased morbidity can be addressed. The importance of treating hyperthermia, glycemic derangements, and hypoxia are discussed above.

Hospital-acquired infection is a frequent complication. Aspiration pneumonia is usually caused by the inability to protect the airway in combination with atelectasis from immobility. Prior to feeding, patients should be screened for swallowing risks and speech pathology should be consulted. Careful attention to silent aspiration and respiratory rate is paramount as tachypnea of > 22 breaths per minute often precedes clinically evident pneumonia. Early mobilization starting within 24 hours is also important in preventing many complications.

Urinary tract infections are usually due to indwelling catheters. These catheters are often unnecessary and should be removed as soon as possible. A rapid urinary catheter protocol can be useful in this regard. Constipation leading to gastrointestinal distress also occurs frequently. Patients should be placed on a bowel regimen from admission with the goal of a bowel movement every other day. Mobilization will also help in this regard.

### ***The Stroke Unit***

The stroke unit seems to be an idea whose time has come, much like the development of the coronary care unit in the past. The idea is that a core multidisciplinary team of professionals who primarily treat stroke patients will produce better outcomes and further research more effectively than a general neurology or medical ward team. In the US and Europe these units have taken a leading role in care and research (38). Evidence has accumulated that they produce improved outcomes by meticulous attention to the details that frequently occur in stroke patients (39,40). The minimum requirements for such a team are a streamlined Emergency Medical System that delivers patients to the emergency department as soon as possible, accurate triage by the emergency department, 24-hour availability of a treating stroke physician (typically a neurologist) and nursing staff, a neurosurgeon, and 24-hour availability of neuroimaging with at least CT (Table 5).

<b>Table 5. Prevention of stroke complications.</b>	
<b>Intervention</b>	<b>Comments</b>
Neuroprotectants	Theoretical benefits thus far depending on agent; negative clinical trials
Control of fever	Fever is known to be harmful in stroke; difficult to achieve hypothermia
Glycemic control	Hyperglycemia is known to be harmful
Deep vein thrombosis prevention	Stroke patients at particularly high risk (e.g. paretic limbs)
Aspiration precautions	Standardized speech pathology examinations
Avoidance of indwelling urinary catheters	Daily review of need for catheters
Bowel regimen	Goal of one bowel movement every other day
Early mobilization	Critical to prevention of complications; start mobilizing patient to chair early in stroke course

## CONCLUSION

Acute ischemic stroke is a treatable condition. Recovery is very time dependent, with intervention required within minutes. In general, the earlier the treatment, the better the outcome. Attention to the “5 Ps” of acute stroke care will allow the treating clinician to logically and systematically approach treatment with an appreciation of underlying disease and pathophysiology. Use of a multidisciplinary stroke team appears essential in coordinating care and improving outcome.

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