

Guidelines for ACUTE STROKE TREATMENT

ACUTE STROKE TREATMENT

Definition of “stroke”

Sudden onset of focal neurological deficit lasting more than 24 hours due to an underlying vascular pathology

Table 8: Definition of stroke severity

TIA and MILD STROKE	MODERATE STROKE	SEVERE STROKE
<p>TIA: Deficits resolve within 24 hours but usually lasts less than 1 hour without evidence of acute infarction on neuroimaging</p> <p style="text-align: center;">or</p> <p>Alert patients with any of the following:</p> <ul style="list-style-type: none"> Mild pure motor weakness of one side of the body, defined as: can raise arm above shoulder, has clumsy hand, or can ambulate without assistance Pure sensory deficit Slurred but intelligible speech Vertigo with incoordination (e.g., gait disturbance, unsteadiness or clumsy hand) Visual field defects alone Combination of (a) and (b) 	<p>Awake patient with significant motor and/or sensory and/or language and/or visual deficit</p> <p style="text-align: center;">or</p> <p>Disoriented, drowsy or stuporous patient, but with purposeful response to painful stimuli</p>	<p>Comatose patient with non-purposeful response, decorticate, or decerebrate posturing to painful stimuli</p> <p style="text-align: center;">or</p> <p>Comatose patient with no response to painful stimuli</p>
<p>See Guidelines for TIA and Mild Stroke</p>	<p>See Guidelines for Moderate Stroke</p>	<p>See Guidelines for Severe Stroke</p>

GUIDELINES FOR TIA AND MILD STROKE

Management Priorities	<p>Ascertain clinical diagnosis of stroke or TIA (history and physical exam are very important)</p> <ul style="list-style-type: none"> • Exclude common stroke mimickers (Appendix I) <p>Provide basic emergent supportive care (ABCs of resuscitation)</p> <p>Monitor neuro-vital signs, BP, MAP, RR, temperature, pupils</p> <p>Perform stroke scales (NIHSS, GCS) (Appendix II)</p> <p>Monitor and manage BP; treat if SBP\geq220 or DBP\geq120 or MAP$>$130 (Appendix III).</p> <p>Precautions:</p> <ul style="list-style-type: none"> • Avoid precipitous drop in BP (BP not $>$20% of baseline MAP) (Appendix III). Do not use rapid-acting sublingual agents; when needed, use easily titratable IV or oral antihypertensive medication • Ensure appropriate hydration. If IVF is needed, use 0.9% NaCl 					
Emergent Diagnostics	<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none;"> <ul style="list-style-type: none"> • Complete blood count (CBC) • Blood sugar (CBG, HGT or RBS) • Electrocardiogram (ECG) </td> <td style="width: 50%; border: none;"> <ul style="list-style-type: none"> • PT/PTT • Plain CT scan of the brain as soon as possible; computation of hematoma volume (Appendix IV) </td> </tr> </table>		<ul style="list-style-type: none"> • Complete blood count (CBC) • Blood sugar (CBG, HGT or RBS) • Electrocardiogram (ECG) 	<ul style="list-style-type: none"> • PT/PTT • Plain CT scan of the brain as soon as possible; computation of hematoma volume (Appendix IV) 		
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Early Specific Treatment	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td colspan="2" style="text-align: center;">Ischemic</td> </tr> <tr> <td style="width: 50%; text-align: center;">Non-cardioembolic (Thrombotic, Lacunar)</td> <td style="width: 50%; text-align: center;">Cardioembolic (Appendix V)</td> </tr> </table>	Ischemic		Non-cardioembolic (Thrombotic, Lacunar)	Cardioembolic (Appendix V)	Hemorrhagic
Ischemic						
Non-cardioembolic (Thrombotic, Lacunar)	Cardioembolic (Appendix V)					

CT Scan Confirmed
(Appendix V)

<p>Aspirin 160-325 mg/day start as early as possible and continue for 14 days (for secondary prevention, see under “Delayed Management and Treatment”)</p> <p>Neuroprotection (Appendix V-D)</p> <p>Early rehabilitation once stable within 72 hours</p>	<p>Consider anticoagulation with IV heparin or SQ low molecular-weight heparin (LMWH) (Appendix VI)</p> <p style="text-align: center;">or</p> <p>Aspirin 160-325 mg/day (if anticoagulation is not possible or contraindicated)</p> <p>Neuroprotection (Appendix V-D)</p> <p>Early rehabilitation once stable within 72 hours</p> <p>If infective endocarditis is suspected, give antibiotics and do not anticoagulate</p>	<p>Early neurology and/or neurosurgeon consult for all ICH is recommended</p> <p>Monitor and maintain BP: MAP 110-130 mmHg (lower limit preferred) (Appendix III)</p> <p>Neuroprotection (Appendix V-D)</p> <p>Early rehabilitation once stable within 72 hours</p> <p>Give anticonvulsants only if with seizures</p> <p>Steroids are not recommended</p>
<p>TIA</p>		<p>Monitor and correct metabolic parameters</p> <p>Correct coagulation / bleeding abnormalities</p> <p>Follow recommendations for neurosurgical intervention (Appendix VII)</p> <p>For aneurysmal SAH, refer to next chapter.</p>
<p>Aspirin 160-325 mg/day</p> <p>If crescendo TIA (multiple events within hours, increasing severity and duration of deficits), consider anticoagulation with IV heparin or SQ LMWH</p>		

CT Scan Not Available

No specific emergent drug treatment recommended
 Neuroprotection (Appendix V-D)
 Consult a neurologist or neurosurgeon
 Early supportive rehabilitation

Place of Treatment

Admit to Hospital (Stroke Unit)	Urgent Outpatient Work-up
1. Stroke onset within 48 hours 2. Patients requiring any specific active intervention, such as: BP control, monitoring and stabilization Cardiac stabilization, including AF, CHF, acute MI Hydration Anticoagulation, if cardioembolic 3. Rapidly worsening deficits 4. Recurrent TIA within the past 2 weeks, especially those with increasing severity and duration of deficits, cardiac arrhythmia, or carotid bruit	1. Single TIA more than 2 weeks 2. Transient monocular blindness alone 3. Stable mild strokes >48 hours from ictus not requiring specific active intervention Advise immediate re-consult or admission if there is worsening of deficit

Delayed Management

Ischemic	Hemorrhagic	
Thrombotic/Lacunar	Cardioembolic	

**and
Treatment
(Secondary
Prevention)**

<p>Control of risk factors</p> <p>Antiplatelets (aspirin, ticlopidine, dipyridamole, extended-release dipyridamole + aspirin combination, clopidogrel, cilostazol) (Appendix VIII)</p> <p>Carotid ultrasound: If this reveals >70% stenosis, refer to neurologist/neurosurgeon/vascular surgeon for decision-making regarding CEA or stenting</p> <p>Recommend transcranial Doppler (TCD) to document intracranial stenosis</p>	<p>Echocardiography and/or cardiology consult</p> <p>If age <75 and PT/INR available, anticoagulation with coumadin (target INR: 2-3)</p> <p>If age >75, aspirin 80-325 mg/day or coumadin (target INR: 2.0 [1.6 – 2.5])</p>	<p>Long-term strict BP control and monitoring</p> <p>Consider angiogram if age <45 years, normotensive, no clear cause of ICH, and/or is a candidate for surgery</p>
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GUIDELINES FOR MODERATE STROKE

Management Priorities

Ascertain clinical diagnosis of stroke (history and physical exam are very important)

- Exclude common stroke mimickers (Appendix I)

Basic emergent supportive care (ABCs of resuscitation)
 Neuro-vital signs, BP, MAP, RR, temperature, pupils
 Perform stroke scales (NIHSS, GCS) (Appendix II)
 Monitor and manage BP; treat if SBP \geq 220 or DBP \geq 120 or MAP $>$ 130 (Appendix III).
 Precaution: Avoid precipitous drop in BP (not $>$ 20% of baseline MAP) (Appendix III). Do not use rapid-acting sublingual agents; when needed use easily titratable IV or oral antihypertensive medication.
 Identify comorbidities (cardiac disease, diabetes, liver disease, gastric ulcer, etc.)
 Recognize and treat early signs and symptoms of increased ICP (Appendix IX)
 Ensure appropriate hydration. If IVF is needed, use 0.9% NaCl

Emergent Diagnostics

- | | |
|--|---|
| <ul style="list-style-type: none"> • CBC • CBG, HGT or RBS • PT/PTT • Serum Na⁺ and K⁺ | <ul style="list-style-type: none"> • ECG • Plain CT scan of brain as soon as possible; computation of hematoma volume (Appendix IV) |
|--|---|

Early Specific Treatment

Ischemic <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border-right: 1px solid black; text-align: center; vertical-align: top;"> Non-cardioembolic (Thrombotic, Lacunar) </td> <td style="width: 50%; text-align: center; vertical-align: top;"> Cardioembolic (Appendix V) </td> </tr> </table>	Non-cardioembolic (Thrombotic, Lacunar)	Cardioembolic (Appendix V)	Hemorrhagic
Non-cardioembolic (Thrombotic, Lacunar)	Cardioembolic (Appendix V)		

CT scan confirmed
(Appendix V)

<p>If within 3 hours of stroke onset, consider IV recombinant tissue plasminogen activator (rtPA) and refer to specialist</p> <p>If within 6 hours of stroke onset and in specialized centers, consider intra-arterial (IA) thrombolysis</p> <p>Aspirin 160-325 mg/day, start as early as possible</p> <p>Neuroprotection (Appendix V-D)</p> <p>Early supportive rehabilitation</p>	<p>If within 3 hours of stroke onset, consider IV rtPA and refer to specialist</p> <p>If within 6 hours of stroke onset and in specialized centers, consider IA thrombolysis</p> <p>Aspirin 160-325 mg/day, start as early as possible</p> <p>If source of embolism can be demonstrated, consider early anticoagulation</p> <p>Neuroprotection (Appendix V-D)</p> <p>Early supportive rehabilitation</p> <p>If infective endocarditis is suspected, give antibiotics and do not anticoagulate</p>	<p>Early neurology and/ or neurosurgical consult for all ICH is recommended</p> <p>Monitor and maintain BP: MAP 110-130 mmHg (lower limit preferred)</p> <p>Neuroprotection (Appendix V-D)</p> <p>Give anticonvulsants only if with seizures</p> <p>Steroids are not recommended</p> <p>Monitor and correct metabolic parameters</p> <p>Correct coagulation/bleeding abnormalities</p> <p>Follow recommendations for neurosurgical intervention (Appendix VII)</p> <p>Early rehabilitation once stable</p> <p>For aneurysmal SAH, refer to next chapter.</p>
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CT scan not available	Likely Ischemic	Likely Hemorrhagic
	No specific emergent drug treatment recommended	Refer to neurologist/neurosurgeon for further diagnostic work-ups and/or subsequent surgery
	Neuroprotection (Appendix V-D)	Neuroprotection (Appendix V-D)
	Refer to neurologist	
	Early supportive rehabilitation	Early supportive rehabilitation

Place of Treatment	Hospital – Intensive Care Unit or Stroke Unit
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Delayed Management and Treatment (Secondary Prevention)	Ischemic		Hemorrhagic
	Thrombotic/Lacunar	Cardioembolic	
	Control of risk factors	Echocardiography and/or cardiology consult	Long-term strict BP control and monitoring
Antiplatelets (aspirin, ticlopidine, dipyridamole, extended-release dipyridamole + aspirin combination, clopidogrel, cilostazol) (Appendix VIII)	INR 2.0 (1.6 – 2.5) If age <75 and PT/INR available, anticoagulation with coumadin (target INR: 2-3)	Consider CT angiography, MRA, or 4-vessel angiography in suspected cases of aneurysm, AV malformation or vasculitis	
Carotid ultrasound: If this reveals >70% stenosis, refer to neurologist/neurosurgeon/vascular surgeon for decision-making regarding CEA or stenting	If age >75, aspirin 80-325 mg/day or coumadin (target INR: 2.0 [1.6 – 2.5])		
Recommend TCD to document intracranial stenosis			

GUIDELINES FOR SEVERE STROKE

Management Priorities

Ascertain clinical diagnosis of stroke (history and physical exam are very important)

- Exclude common stroke mimickers (Appendix I)

Basic emergent supportive care (ABCs of resuscitation)

Neuro-vital signs, BP, MAP, RR, temperature, pupils

Perform stroke scales (NIHSS, GCS) (Appendix II)

Monitor and manage BP; treat if SBP \geq 220 or DBP \geq 120 or MAP $>$ 130 (Appendix III).

Precautions:

- Avoid precipitous drop in BP (not $>$ 20% of baseline MAP) (Appendix III). Do not use rapid-acting sublingual agents; when needed, use easily titratable IV or oral antihypertensive medication (Appendix IIIB)

Identify comorbidities (cardiac disease, diabetes, liver disease, gastric ulcer, etc.)

Recognize and treat early signs and symptoms of increased ICP (Appendix IX)

Ensure appropriate hydration. If IVF is needed, use 0.9% NaCl

Emergent Diagnostics

- CBC
- CBG, HGT or RBS
- PT/PTT

- Serum Na⁺ and K⁺
 - ECG
- Plain CT scan of brain; computation of hematoma volume (Appendix IV)

Early Specific Treatment

Ischemic	Hemorrhagic
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CT scan confirmed (Appendix V)	Non-cardioembolic (Thrombotic)	Cardioembolic (Appendix V)	
	<p>May give aspirin 160-325 mg/day</p> <p>In posterior circulation strokes within 6 hour of onset, consider IA thrombolysis and refer to specialist</p> <p>Neuroprotection (Appendix V-D)</p> <p>If cerebellar infarct, consult neurosurgeon as soon as possible</p> <p>Early supportive rehabilitation</p>	<p>May give aspirin 160-325 mg/day</p> <p>In posterior circulation strokes within 6 hours of onset, consider IA thrombolysis and refer to specialist</p> <p>Neuroprotection (Appendix V-D)</p> <p>If cerebellar infarct, consult neurosurgeon as soon as possible</p> <p>Early supportive rehabilitation</p>	<p>Supportive treatment:</p> <ol style="list-style-type: none"> 1. Mannitol 20% 0.5 - 1 g/kgBW q 4-6 hours for 3-7 days 2. Neuroprotection (Appendix V-D) <p>Neurosurgery consult if:</p> <p>Patient not herniated; bleed located in putamen, pallidum, cerebellum; family is willing to accept consequences of irreversible coma or persistent vegetative state and goal is reduction of mortality (Appendix VII)</p> <ol style="list-style-type: none"> 2. ICP monitoring is contemplated and salvage surgery is considered <p>Early supportive rehabilitation</p>

CT scan not available	<p>No specific emergent drug treatment recommended</p> <p>Neuroprotection (appendix V-D)</p> <p>Refer to neurologist</p>
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Place of Treatment	Intensive Care Unit
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Delayed Management and Treatment	Discuss prognosis with relatives of the patient in most compassionate manner		
	Ischemic		Hemorrhagic
	Thrombotic	Cardioembolic	

(Secondary Prevention)

<p>Control of risk factors</p> <p>Antiplatelets (Aspirin, ticlopidine, dipyridamole, extended-release dipyridamole + aspirin combination, clopidogrel or cilostazol) (Appendix VIII)</p>	<p>Echocardiography and/or cardiology consult</p> <p>If age <75 and PT/INR available, anticoagulation with coumadin (target INR=2.0-3.0)</p> <p>If age >75, aspirin 80-325 mg/day or coumadin with target INR 2.0 (1.6-2.5)</p>	<p>Long-term strict BP control and monitoring</p> <p>Consider CT angiography, MRA, or 4-vessel angiography in suspected cases of aneurysm, AV malformation or vasculitis</p>
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APPENDIX I

Differential Diagnoses of Stroke

- A. The presence of any of the following should alert the physician to consider conditions other than stroke:
- Gradual progressive course and insidious onset
 - Pure hemifacial weakness including forehead (Bell's palsy)
 - Trauma
 - Fever prior to onset of symptoms
 - Recurrent seizures
 - Weakness with atrophy
 - Recurrent headaches (migraine, tension-type headache)
- B. Conditions that mimic stroke in the emergency department (according to decreasing frequency):
1. Seizures
 2. Systemic infection
 3. Brain tumor
 4. Toxic-metabolic
 5. Positional vertigo
 6. Cardiac
 7. Syncope
 8. Trauma
 9. Subdural hematoma
 10. Herpes encephalitis
 11. Transient global amnesia
 12. Dementia
 13. Demyelinating disease
 14. Cervical spine fracture
 15. Myasthenia gravis
 16. Parkinsonism
 17. Hypertensive encephalopathy
 18. Conversion disorder

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Libman RB, Wirkowski E, Alvir J, Rao H. Conditions that mimic stroke in the emergency department. *Arch Neurol* 1995;52:1119-1122.

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APPENDIX II

Stroke Scales

I. Glasgow Coma Scale

Category	Score
Eye Opening	
Spontaneous	4
To speech	3
To pain	2
None	1
Best Motor Response	
Obeys	6
Localizes	5
Withdraws	4
Abnormal flexion (decorticate)	3
Abnormal extension (decerebrate)	2
None	1
Best Verbal response	
Oriented	5
Confused	4
Inappropriate words	3
Incomprehensible sounds	2
None	1

Total score=15

II. National Institutes of Health (NIH) Stroke Scale

Items	Scale Definition
Ia. Level of Consciousness (LOC)	0 = Alert, keenly responsive 1 = Not alert, but arousable by minor stimulation to obey, answer or respond 2 = Not alert, requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped) 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, or totally unresponsive, flaccid, areflexic
Ib. LOC Questions	0 = Answers both questions correctly 1 = Answers one question correctly 2 = Answers neither question correctly
Ic. LOC Commands	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly

2. Best gaze	<p>0 = Normal</p> <p>1= Partial gaze palsy. Gaze is abnormal in one or both eyes but forced deviation or total gaze paresis is not present</p> <p>2 = Forced deviation, or total gaze paresis is not overcome by oculocephalic maneuver</p>
3. Visual	<p>0 = No visual loss</p> <p>1 = Partial hemianopia</p> <p>2 = Complete hemianopia</p> <p>3 = Bilateral hemianopia (blind, including cortical blindness)</p>
4. Facial palsy	<p>0 = Normal symmetrical movement</p> <p>1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling)</p>
5. Motor (Arm) 5 a. Left arm 5 b. Right arm	<p>0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds</p> <p>1 = Drifts; limb holds 90 (or 45) degrees but drifts down before full 10 seconds; does not hit bed or other support</p> <p>2 = Some effort against gravity, limb cannot get up to or maintain (if cued) 90 (or 45) degrees; drifts down to bed, but has some effort against gravity</p> <p>3 = No effort against gravity; limb falls</p> <p>4 = No movement</p> <p>9 = Amputation or joint fusion; explain</p>
6. Motor (Leg) 6 a. Right leg 6 b. Left leg	<p>0 = No drift; leg holds 30-degree position for full 5 seconds</p> <p>1 = Drifted; leg falls by the end of the 5-second period but does not hit bed</p> <p>2 = Some effort against gravity; leg falls to bed by 5 seconds but has some effort against gravity</p> <p>3 = No effort against gravity; leg falls to bed immediately</p> <p>4 = No movement</p> <p>9 = Amputation or joint fusion; explain</p>
7. Limb ataxia	<p>0 = absent</p> <p>1 = Present in one limb</p> <p>2 = Present in two limbs</p> <p>9 = Amputation or joint fusion; explain</p>
8. Sensory	<p>0 = Normal; no sensory loss</p> <p>1 = Mild to moderate sensory loss; patient feels pinprick is less sharp or dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware he/she is being touched</p> <p>2 = Severe or total sensory loss; patient is not aware of being touched in the face, arm or leg</p>

9. Best Language	<p>0 = No aphasia</p> <p>1 = Mild to moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation on provided material difficult</p> <p>2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning and guessing by the listener. Range of information that can be exchanged is limited; listener carries the burden of communication</p> <p>3 = Mute, global aphasia; no usable speech or auditory comprehension</p>
10. Dysarthria	<p>0 = Normal</p> <p>1 = Mild to moderate; patient slurs at least some words and at worst, can be understood with some difficulty</p> <p>2 = Severe; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric</p> <p>9 = intubated or other physical barrier; explain</p>
11. Extinction & Inattention	<p>0 = No abnormality</p> <p>1 = Visual, tactile, auditory, spatial or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities</p> <p>2 = Profound hemiattention or hemi-inattention to more than one modality. Does not recognize own hand or orients to only one side of space</p>

Total score=42

III. Modified Rankin Scale

	Score
No symptoms at all	0
No significant disability despite symptoms; able to carry out all usual duties and activities	1
Slight disability ; unable to carry out all previous activities but able to look after own affairs without assistance	2
Moderate disability ; requiring some help but able to walk without assistance	3
Moderately severe disability ; unable to walk without assistance and unable to attend to own bodily needs without assistance	4
Severe disability ; bedridden, incontinent and requiring constant nursing care and attention	5

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APPENDIX III

Blood Pressure Management

A. BP management in Acute Ischemic Stroke

1. Use the following definitions:

Cerebral Perfusion Pressure (CPP) = MAP – ICP

$$\text{MAP} = \frac{2 (\text{diastolic}) + \text{systolic}}{3}$$

2. Check if patient is in any condition that may increase BP such as pain, stress, bladder distention or constipation, which should be addressed accordingly.

3. Allow “permissive hypertension” during the first week to ensure adequate CPP but ascertain cardiac and renal protection

a. Treat if SBP \geq 220 or DBP \geq 120 or MAP $>$ 130

b. Defer emergency BP therapy if MAP is within 110-130 or SBP=185-220 mmHg or DBP=105-120 mmHg, unless in the presence of:

- Acute MI
- Congestive heart failure
- Aortic dissection
- Acute pulmonary edema
- Acute renal failure
- Hypertensive encephalopathy

4. Treat with small doses of IV antihypertensives patients who are potential candidates for rtPA therapy who have persistent elevations in SBP $>$ 185 mmHg or DBP $>$ 110 mmHg. Maintain BP just below these limits.

5. Use the following locally available intravenous anti-hypertensives in acute stroke:

Drug	Dose	Onset of Action	Duration of Action	Availability /Dilution	Stability	Adverse Reactions	Action
Nicardipine	1-15 mg/hour	5-10 mins	1-4 hours	(10 mg/ 10 ml amp); 10 mg in 90 ml NSS/D5W	1 to 4 hours	Tachycardia, headache, flushing, dizziness, somnolence, nausea	Inhibits calcium ion from entering slow channel, producing coronary, vascular, smooth muscle relaxation & vasodilatation

Hydralazine	IV push 10-20 mg/dose q 4-6 hours as needed, may increase to 40 mg/dose	10-20 mins	3-8 hours	25 mg/mL amp; 25 mg/tab	4 days	Tachycardia, flushing, headache, vomiting, increased angina	Direct vasodilatation of arterioles & decreased systemic resistance
Labetalol	5 mg IV push over 2 mins, repeat with incremental dose of 10, 20, 40, 80 mg until desired BP is achieved or a total dose of 300 mg has been administered	2-5 mins	2-4 hours	5 mg/ml in 40 ml vial; 250 mg in 250 mL NSS/D5W	72 hours	Orthostatic hypotension, drowsiness, dizziness, lightheadedness, dyspnea, wheezing & bronchospasm	Alpha- & beta-blocker. Beta-adrenergic blocking activity is 7x > than alpha-adrenergic blockers. Produces dose-dependent ↓ in BP without significant ↓ in HR or cardiac output
Esmolol	0.25-0.5 mg/kg IV push 1-2 mins followed by infusion of 0.05 mg/kg/min. If there is no response, repeat 0.5 mg/kg bolus dose & ↑ infusion to 0.10 mg/kg/min. Maximum infusion rate=0.30 mg/kg/min	2-10 mins	10-30 mins	100 mg/10 ml vial; 2,500 mg in 250 mL D5W/NSS	48 hours	Hypotension, bradycardia, AV block, agitation, confusion, wheezing / bronchoconstriction, phlebitis	Short-acting beta-adrenergic blocking agent. At low doses, has little effect on beta2 receptors of bronchial & vascular smooth muscle

B. Blood pressure management in Acute Hypertensive ICH

Maintain MAP < 130, but not lower than 110 mmHg

- Sustained hypertension may alter cerebral autoregulation, promote progression of bleed and increase edema
- Hypotension may result in cerebral hypoperfusion especially in the setting of increased intracranial pressure (ICP)
- Absence of penumbra allows for more aggressive BP management

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APPENDIX IV

Neuroimaging (CT and MRI)

A. Hyperacute or Acute Ischemic Stroke

- Plain CT scan of the head is the initial neuroimaging study of choice in acute stroke. The main objective is to exclude hemorrhagic stroke and stroke mimickers. A plain study obviates the need to wait for creatinine result.
- CT scan is 100% sensitive in documenting intracranial hemorrhage (ICH) and 96% sensitive in documenting subarachnoid hemorrhage (SAH).
- Cerebral infarcts are often not documented within 3 hours from stroke onset. However, 60% have “early” infarct signs when viewed very closely:
 1. Dense MCA sign
 2. Obscuration of the lentiform nucleus
 3. Loss of the gray-white interphase along the lateral insula (Insular ribbon sign)
 4. Effacement of the sulci
- In cases of neurologic deterioration, large infarcts or suspected hemorrhagic conversion, a follow-up plain CT of the head is recommended.
- MRI has the technical advantage of documenting small lesions or those located in the brainstem or posterior fossa.
- MRI can detect early infarction as early as 90 minutes using Diffusion Weighted Imaging (DWI).
- Despite the superior diagnostic yield of MRI over CT, MRI is not recommended as routine evaluation of patients with acute ischemic stroke. It is more expensive, time-consuming and less readily available.

B. Intracerebral Hemorrhage

- CT can accurately document the exact location of the hemorrhage and the presence of mass effect, ventricular extension and hydrocephalus.
- In hypertensive ICH, a repeat plain CT scan after 24 hours of ictus is recommended especially in cases showing clinical deterioration to document hematoma enlargement and/or development of hydrocephalus.

Computation of Hematoma Volume (Kothari method)

$$\text{Hematoma volume (in cc)} = \frac{A \times B \times C}{2}$$

where: A= Largest diameter of hematoma (in cm)
 B= Diameter perpendicular to A (in cm)
 C= Number of slices on CT scan with hemorrhage X slice thickness (in cm)

- Count slice as 1 if size of hematoma is >75% of largest diameter
 - Count slice as 0.5 if size of hematoma is 25-75% of largest diameter
 - Disregard slice if size of hematoma is <25% of largest diameter
- In suspected cases of AV malformation, aneurysm or tumor bleed, a contrast CT of the head may be warranted

C. Subarachnoid Hemorrhage

- Plain CT of the head is strongly recommended as the initial procedure for diagnosis.
- The diagnostic yield of CT goes down from 92% within the first 24 hours to 50% within 7 days of onset.

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APPENDIX V

Early Specific Treatment For Ischemic Stroke

A. Thrombolytic therapy

- Patients treated with IV recombinant tissue plasminogen activator (rtPA) within 3 hours of stroke onset are at least 30% more likely to have minimal or no disability at 3 months.
- Streptokinase has no role in acute thrombolysis for ischemic stroke .

National Institute of Neurological Disorders and Stroke (NINDS) rTPA guidelines

1. Dose of rtPA is 0.9 mg/kg (maximum 90 mg). Ten percent of total dose is given as IV bolus, the rest as infusion over 60 minutes.
2. rtPA is recommended within 3 hours of onset of ischemic stroke. The benefit of IV rtPA for acute ischemic stroke beyond 3 hours from onset of symptoms is not established. IV rtPA is not recommended when the time of onset of stroke cannot be ascertained reliably, including strokes recognized upon awakening.
3. Thrombolytic therapy is not recommended unless the diagnosis is established by a physician with expertise in diagnosing stroke and CT of the brain is assessed by physicians with expertise in reading this imaging study. If CT demonstrates early changes of a recent major infarction such as sulcal effacement, mass effect, edema or possible hemorrhage, thrombolytic therapy should be avoided.
4. Thrombolytic therapy cannot be recommended for patients with any of the following (NINDS Study):
 - a. Current use of oral anticoagulants or PT>15 seconds (INR>1.7)
 - b. Use of heparin in the previous 48 hours or prolonged PTT>1.5x normal
 - c. Platelet count <100,000 mm³
 - d. Another stroke or a serious head injury within the previous 3 months
 - e. Major surgery within the preceding 14 days
 - f. Sustained pretreatment SBP>185 mmHg or DBP>110 mmHg (when aggressive treatment necessary to lower BP)
 - g. Rapidly improving neurological signs
 - h. Mild, isolated neurological deficits, such as ataxia alone, sensory loss alone, dysarthria alone, or minimal weakness
 - i. Prior ICH
 - j. Blood glucose <50 mg/dL or > 400 mg/dL
 - k. Seizure at onset of stroke
 - l. Gastrointestinal or urinary bleeding within preceding 21 days
 - m. Recent myocardial infarction (within the previous 3 months)

5. Thrombolytic therapy should not be given unless emergent ancillary care and the facilities to handle bleeding complications are readily available.
6. Caution is advised before giving rtPA to persons with severe stroke (NIH Stroke Scale Score >22)
7. Because the use of thrombolytic drugs carries the real risk of major bleeding, whenever possible the risks and potential benefits of rtPA should be discussed with the patient and his or her family before treatment is initiated.
8. Patients given rtPA should not receive antiplatelets or anticoagulants within 24 hours of treatment.

B. Antithrombotic therapy

1. International Stroke Trial (IST)
 - Multicenter randomized clinical trial of 19,435 patients
 - Regimen: Aspirin 300-325 mg/day vs. no aspirin
Heparin SC vs. no heparin
5,000 units bid or 12,500 units bid
 - Started within 48 hours of stroke onset for 14 days or until discharge
 - Results:
 - Aspirin
 - Fewer recurrent stroke within 14 days
 - Fewer deaths and dependency at 6 months
 - Heparin
 - No benefit even at 6 months
 - If used should not exceed 5,000 units bid
2. Chinese Acute Stroke Trial (CAST)
 - 21,106 patients randomized
 - Aspirin 160 mg/day vs. placebo
 - Started within 48 hours of stroke onset
 - Results:
 - Risk of recurrent stroke or vascular death:
 - Aspirin 5.3%
 - Placebo 5.9% (p=0.03)
3. Meta-analysis on low molecular-weight heparin (LMWH) and heparinoids in acute ischemic stroke involving 2,855 patients has shown that treatment was associated with significant reduction in venous thromboembolism (DVT and pulmonary embolism). LMWH has no significant effect on reducing death and disability at 6 months. Symptomatic ICH was not significantly increased.

C. Neuroprotection

1. Neuroprotective Interventions: The 5 "H" Principle

Avoid hypotension, hypoxemia, hyperglycemia or hypoglycemia and hyperthermia (fever) during acute stroke in an effort to "salvage" the ischemic penumbra

Avoid Hypotension

- Aggressive BP lowering is detrimental in acute stroke. Manage hypertension as per recommendation ([Appendix III](#))

Avoid Hypoxemia

- Routine oxygenation in all stroke patients is not warranted
- Maintain adequate tissue oxygenation (target O₂ saturation >95%)
- Do arterial blood gases (ABG) determination or monitor oxygenation via pulse oximeter
- Give supplemental oxygen if there is evidence of hypoxemia or desaturation
- Provide ventilatory support if upper airway is threatened or sensorium is impaired or ICP increased.

Avoid hypoglycemia or hyperglycemia

- Hyperglycemia can increase the severity of ischemic injury (causes lactic acidosis, increases production of free radicals, worsens cerebral edema and weakens blood vessels), whereas hypoglycemia can mimic a stroke
- Prompt determination of blood glucose should be done in all stroke patients
- Ensure tight glycemic control at 80-110 mg/dL
- Avoid glucose-containing (D5) IV fluids. Use isotonic saline (0.9% NaCl)

Avoid Hyperthermia

- Fever in acute stroke is associated with poor outcome possibly related to increased metabolic demand, increased free radical production and enhanced neurotransmitter release.
- For every 1°C increase in body temperature, the relative risk of death or disability increases by 2.2.
- Search for the source of fever.
- Treat fever with antipyretics and cooling blankets.
- Maintain normothermia.

D. Neuroprotectants

Neuroprotectants are drugs that:

- Protect against excitotoxins and prolong neuronal survival
- Block the release of glutamate, free radicals, inflammatory cytokines, and the accumulation of intracellular calcium cations.

Several neuroprotective drugs have reached phase III clinical trials, but most had negative or disappointing results except for citicoline. Data-pooling analysis on four trials involving 1,652 patients with ischemic stroke show that treatment with citicoline within the first 24 hours increases the probability of global recovery (NIHSS, mRS, BI) by 30% at 3 months.

CDP–choline helps increase phosphatidylcholine synthesis and inhibition of phospholipase A2 within the injured brain during ischemia

Several phase III clinical trials (e.g. SAINT II, FAST-MAG) are currently underway

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APPENDIX VI

Anticoagulation In Acute Cardioembolic Stroke

A. Cardioembolic sources

High Risk	Low or Uncertain Risk
AF (valvular or non-valvular)	Mitral valve Prolapse
Rheumatic mitral stenosis	Mitral annular calcification
Prosthetic heart valves	Patent foramen ovale (PFO)
Recent MI	Atrial septal aneurysm
LV/LA thrombus	Calcific aortic stenosis
Atrial myxoma	Mitral valve strands
Infective Endocarditis	
Dilated cardiomyopathy	
Marantic endocarditis	

B. Indications and contraindications for anticoagulation in patients with cardioembolic stroke

Probably Indicated	Contraindicated
Intracardiac thrombus	Bleeding diathesis
Mechanical prosthetic valve	Non-petechial intracranial hemorrhage
Recent MI	Recent major surgery or trauma
CHF	Infective endocarditis
Bridging measure for long term anticoagulation	

C. When considering anticoagulation in acute cardioembolic stroke, the benefits of anticoagulation in reducing early stroke recurrence should be weighed against the risk of hemorrhagic transformation. The latter is higher in patients with large infarction, severe strokes or neurological deficits and uncontrolled hypertension.

D. How to anticoagulate

1. Requirements for IV anticoagulation of patients with cardiogenic source of embolism:
 - a. Heparin sodium in D5W
 - b. Infusion pump, if available
 - c. Activated partial thromboplastin time (aPTT) or clotting time
2. Procedure:
 - a. Start intravenous infusion at 800 units heparin/hour ideally using infusion pump. IV heparin_{bolus} is not recommended.

- b. Perform aPTT as often as necessary, every 6 hours if need, to keep aPTT at 1.5-2.5x the control. Risk for major hemorrhage, including intracranial bleed, progressively increases as aPTT exceeds 80 seconds.
- c. Infusion may be discontinued once oral anticoagulation with coumadin has reached therapeutic levels or once antiplatelet medication is started for secondary prevention.

To date, there has been no trial directly comparing efficacy of unfractionated heparin vs LMWH in patients with acute cardioembolic stroke. LMWH has the advantage of ease of administration and does not require aPTT monitoring.

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APPENDIX VI

Early Specific Treatment of Hypertensive Intracerebral Hemorrhage

A. Medical Treatment for all ICH:

The goals are to prevent complications and carefully manage BP.

- a. Maintain MAP <130, but not lower than 110 mmHg
- b. Manage increased ICP accordingly (see Appendix IX)
- c. Start anticonvulsants only if with seizures
 - The incidence of seizures is higher in ICH, especially in lobar hematomas.
 - The role of prophylactic anticonvulsants in deep hemorrhages is unclear. It is justified to withhold anticonvulsants until clinically indicated.
- d. Prevent and treat respiratory complications. Endotracheal intubation is performed in patients to provide airway protection and in those in coma or with respiratory failure.
- e. Prevent and treat infections.
- f. Maintain adequate nutrition.
- g. Ensure proper fluid and electrolyte balance; maintain normothermia and normoglycemia.
- h. Rehabilitate early once stable.
- i. Practice bedside precautions.
- j. Deep-vein thrombosis and pulmonary embolism prophylaxis should be instituted (use antiembolic stockings or intermittent pneumatic compression devices)

B. Surgical Treatment

Its role depends on the size, extent and location of the hematoma, and patient factors.

- a. There is evidence of increase in hematoma size by 33% within 24 hours of stroke onset in 38% of cases.
- b. Considerations for surgical intervention:

Non-surgical candidates

- Patients with small hemorrhages (<10 mL) or minimal neurological deficits
- Patients with GCS<5 except those who have cerebellar hemorrhage and brainstem compression
- Patients with hematoma volume > 85 mL

Candidates for immediate surgery

- Patients with cerebellar hemorrhage >3 cm who are neurologically deteriorating or have brainstem compression and hydrocephalus from ventricular obstruction

- Patients with bleed associated with a structural lesion such as an aneurysm, AV malformation or cavernous angioma if there is a chance for good outcome and the vascular lesion is surgically accessible
- Clinically deteriorating young patients with moderate or large lobar hemorrhage.
- Ventricular drainage for patients with intraventricular hemorrhage with moderate to severe hydrocephalus.

All other patients may benefit from surgery

- Patients with basal ganglia or thalamic hemorrhage
- Patients with GCS >4
- Patients with supratentorial hematoma with volume >30 cc

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APPENDIX VIII

Antiplatelets for Secondary Stroke Prevention

A. Aspirin

1. Antiplatelet Trialist's Collaboration
 - 65 trials involving 60,196 patients with symptomatic atherosclerosis (e.g., unstable angina, MI, TIA, stroke)
 - Aspirin 50-1,500 mg/day vs control
 - 23% odds reduction on composite outcome of MI, stroke or vascular death
 - Highest RRR was seen in the low (75-150 mg) and medium dose (160-325 mg) groups
2. Mini-meta-analysis on aspirin among patient with prior stroke or TIA
 - 10 trials involving 6,171 patients with prior TIA or non-disabling stroke
 - Aspirin reduced the odds for the cluster of stroke, MI or vascular death by 16%
 - No difference in RRR for low (<100 mg), medium (300-325 mg) and high doses (>900 mg) of aspirin

B. Ticlopidine

1. Canadian American Ticlopidine Study (CATS)
 - 1,072 patients with recent thromboembolic stroke
 - Ticlopidine 250 mg bid vs placebo
 - 30.2% risk reduction on composite outcome of MI, stroke, vascular death over placebo
2. Ticlopidine Aspirin Stroke Study (TASS)
 - 3,069 patients with recent TIA/cerebral infarction
 - Ticlopidine 250 mg bid vs aspirin 1,300 mg od
 - 12% risk reduction vs aspirin for stroke or death at 3 years

C. Clopidogrel

1. Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE)
 - 19,185 patients with prior stroke, MI or PAD
 - Clopidogrel 75 mg/day vs aspirin 325 mg/day
 - 8.7% RRR vs aspirin for combined endpoint of stroke, MI and vascular death
2. Clopidogrel and Aspirin combination (Management of Atherothrombosis with Clopidogrel in High-Risk Patients with TIA or Stroke [MATCH])
 - 7,599 patients with prior stroke or TIA and additional risk factors
 - Clopidogrel-aspirin 75 mg/75 mg vs clopidogrel 75 mg
 - No significant difference in composite outcome of ischemic stroke, MI, vascular death or rehospitalization secondary to ischemic events

3. Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA)

- 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors
- Clopidogrel 75 mg with low-dose aspirin (75-162 mg) vs low-dose aspirin only
- Overall, clopidogrel/aspirin combination was not significantly more effective than aspirin alone in reducing rate of MI, stroke or vascular death
- Suggestion of benefit with combination treatment in patients with symptomatic atherothrombosis

D. Cilostazol

Cilostazol Stroke Prevention Study (CSPS)

- 1,095 patients with cerebral infarction in the past 6 months
- Cilostazol 100 mg bid vs placebo
- 41.7% RRR for recurrent stroke

E. Dipyridamole and aspirin combination

1. European Stroke Prevention Study (ESPS 2)

- 6,602 patients with recent TIA or stroke randomized to placebo, aspirin 25 mg bid, extended-release dipyridamole 200 mg bid, or aspirin 25 mg + ER-dipyridamole 200 mg bid
- Aspirin better than placebo; dipyridamole better than placebo; **combination treatment better than either agent alone.**
- 37.8% risk reduction for stroke with combination therapy over placebo
- No increased risk of major bleeding with combination treatment

2. European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT Trial)

- 2,739 patients with recent TIA or minor stroke of arterial origin randomized to aspirin 30-325 mg/day or aspirin 30-325 mg od + dipyridamole 200 mg bid
- 20% risk reduction for composite outcome of stroke, MI, vascular death with combination therapy
- No increased risk of major bleeding with combination treatment

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APPENDIX IX

Management of Increased Intracranial Pressure

A. Signs and symptoms of increased ICP

1. Deteriorating level of sensorium
2. Cushing's triad
 - i. Hypertension
 - ii. Bradycardia
 - iii. Irregular respiration
3. Anisocoria

B. Management options for increased ICP

General

1. Control agitation and pain with short-acting medications, such as NSAIDs and opioids.
2. Control fever. Avoid hyperthermia.
3. Control seizures if present. May treat with phenytoin with a loading dose of 18-20 mg/kg IV then maintained at 3-5 mg/kg. Status epilepticus should be managed accordingly.
4. Strict glucose control between 80-110 mg/dL
5. No dextrose-containing IVF. Hyperglycemia may extend ischemic zone (penumbra) and further cause cerebral edema
6. Use stool softeners to prevent straining.

Specific

1. Elevate the head at 30 to 45 degrees to assist venous drainage.
2. Give osmotic diuretics: Mannitol 20% loading dose at 1 g/kg, maintenance dose at 0.5-0.75 mg/kg) to decrease intravascular volume and free water.
3. Lost fluids must be replaced. Hypertonic saline is an option and has the advantage of maintaining an effective serum gradient for a prolonged period with lower incidence of rebound intracranial hypertension. Aim for serum osmolarity=310 mOsm/L. (Serum osmolarity = 2 (Na) + Glucose/18 + BUN /2.8)
4. Hyperventilate only in impending herniation by adjusting tidal volume and pCO₂ between 25 to 30. This maneuver is usually effective only for approximately 6 hours. Otherwise maintain normal pCO₂ between 35 and 40.
5. Carefully intubate patients with GCS 8 or less, or those unable to protect the airway.
6. Do CSF drainage in patients with intraventricular hemorrhage (IVH) or hydrocephalus.
7. Use barbiturates if all other measures fail. Available locally is thiopental (loading dose=10 mg/kg, maintenance dose titrated at 1-12 mg/kg/hour continuous infusion to achieve burst suppression pattern in EEG)

8. Consider surgical evacuation for mass lesions.
9. Consider decompressive hemicraniectomy in cases of malignant middle cerebral artery infarcts

C. Sedatives and Narcotics Available Locally

Drugs	Usual Dose	Onset of Action	Duration of Effect	Comments	Availability/Dilution
Midazolam	0.025-0.35 mg/kg	1 to 5 min	2 hours	Unpredictable sedation	15 mg/3 mL amp; 5 mg/5 mL amp; 50 mg in 100 mL NSS/D5W
Diazepam	0.1-0.2 mg/kg	Immediate	20 to 30 minutes	Sedation can be reversed with flumazenil (0.2-1 mg at 0.2 mg/min at 20 min interval, max dose 3 mg in one hour)	10 mg/2 mL amp; 50 mg in 250 mL NSS/D5W
Propofol	5-50 ug/kg/min	<40 secs	10 to 15 min	Expensive	(10 mg/mL) 100 mL vial (premixed)
Ketorolac	50-100 mg IV	1 hour	6 to 8 hours	NSAID	30 mg/mL amp
Tramadol	50-100 mg IV	1 hour	9 hours	Centrally acting synthetic analgesic compound not chemically related to opiates but thought to bind to opioid receptors and inhibit reuptake of NE and serotonin	50 mg/ 2 mL amp; 100 mg/2 mL amp
Fentanyl	50-100 ug/hour	1-2 mins	>60 min	Can be easily reversed with naloxone (0.4-2 mg IVP; repeat at 2-3 min intervals, max dose 10 mg) * 110x more potent than morphine	100 ug/2 mL; 2,500 ug in 250 mL NSS/D5W
Morphine	2-5 mg/hour	5 mins	>60 min	Opioid	10 mg/mL gr 1/6; 16 mg/ mL gr 1/4

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