Introduction
Emanating from the results of the original National Institute of Neurological Disorders and Stroke recombinant tissue plasminogen activator (NINDS rt-PA) trial [1], the management of acute stroke has evolved as a cornerstone of emergency medical care, hospital medicine, and clinical neurology. While the only treatment for acute ischemic stroke approved by the US Food and Drug Administration (FDA) remains intravenous (IV) rt-PA administered within 3 hours of symptom onset, the field continues to expand with a focus on more timely treatment, expanding the pool of patients eligible for treatment, and optimization of methods of reperfusion. These advances include the use of IV rt-PA beyond the 3-hour window, the direct administration of intra-arterial rt-PA, and implementation of a variety of devices aimed at mechanical thrombectomy and other interventional means of cerebrovascular recanalization. However, integrating all of the scientific evidence guiding the acute stroke paradigm is daunting, even for the most seasoned vascular neurologist. According to the National Guideline Clearinghouse, an initiative of the Agency for Healthcare Research and Quality in the Department of Health and Human Services, there are currently 225 published guidelines related to “acute stroke” from various organizations and societies around the world [2]. The current standard of stroke care in the US is guided by the American Heart Association/American Stroke Association’s (AHA/ASA) Get With the Guidelines (GWTG) program [3].

While stroke therapeutics will be discussed in detail elsewhere in this book, the aim of this chapter is to offer a simple, practical approach to the bedside evaluation of the acute stroke patient. As the opinions and recommendations herein draw on experience treating acute stroke, they also reflect the literature and guiding evidence. The chapter will broadly highlight seminal studies, published AHA/ASA guidelines, FDA regulations, and The Joint Commission (TJC) certification requirements for primary/comprehensive stroke centers - links to further resources can be found in the Appendix, Chapter 9. Explored in detail will be the various issues facing neurologists or other physicians in acute stroke scenarios, including an accurate gathering of history, essentials of the acute stroke physical exam, radiological diagnosis, and potential hurdles precluding a treatment decision. While these necessary steps are very much protocol driven, the reality of the acute stroke setting dictates a somewhat simultaneous process in order to achieve the efficient delivery of treatment. Ultimately, the aim of the chapter is to further promote rapid diagnosis and timely management for all acute stroke patients, as the medical community continues to strive for the best possible outcomes from this disabling and deadly disease.

Is it a stroke?
Despite rapid advances in neuroimaging over the past 20 years, the bedrock of the evaluation of the acute stroke patient remains sound clinical diagnosis. The physician is frequently asked to see a
patient in urgent consultation for treatment of acute stroke in the absence of a firmly established diagnosis. Even with the advent of highly advanced neuroimaging techniques, stroke remains a clinical diagnosis; as opposed to an infarct, which is an imaging or tissue-based diagnosis. Stroke is, by definition, the acute onset of a persistent focal neurological deficit or constellation of deficits referable to a specific cerebrovascular territory. The absence of abrupt onset of symptoms all but precludes acute stroke as the diagnosis. Symptoms that do not all fit into a specific vascular territory suggest either a diagnosis other than stroke or the possibility of multifocal ischemia as may be seen in cardioembolism. Additionally, stroke typically produces negative symptoms—that is to say, loss of strength, sensation, vision, or other neurological function. Presence of positive symptoms (paresthesias, involuntary movements, visual phenomena) is uncommon in stroke, unless the patient with a cortical stroke is having a concurrent seizure or occasionally a triggered migraine— as in cervical artery dissection.

Ischemic stroke subtypes in specific vascular territories tend to produce fairly predictable constellations of signs and symptoms, or “syndromes” [4]. Rapid recognition of these syndromes is crucial in early diagnosis and timely treatment of acute stroke or, often of equal importance, the elimination of stroke as a potential diagnosis. In terms of broadly defined clinical stroke syndromes, one can consider large vessel versus small vessel presentations. Generally speaking, large vessel strokes tend to occur in the setting of atherosclerotic and/or embolic disease, whereas small vessel (lacunar) strokes tend to present in the setting of chronic small vessel occlusive disease related primarily to chronic hypertension and diabetes. The clinical manifestations of commonly encountered large vessel syndromes are described in Table 1.1.

<table>
<thead>
<tr>
<th>Vascular territory</th>
<th>Signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal carotid artery (ICA)</td>
<td>Combined ACA/MCA syndromes; ipsilateral monocular visual loss secondary to central retinal artery occlusion (amaurosis); branch retinal artery occlusions may present as ipsilesional altitudinal field cuts</td>
</tr>
<tr>
<td>Left anterior cerebral artery (ACA)</td>
<td>Right leg numbness and weakness, transcortical motor aphasia, and possibly ipsilesional or contralesional ideomotor apraxia</td>
</tr>
<tr>
<td>Right ACA</td>
<td>Left leg numbness and weakness, motor neglect, and possibly ipsilesional or contralesional ideomotor apraxia</td>
</tr>
<tr>
<td>Left middle cerebral artery (MCA)</td>
<td>Right face/arm &gt; leg numbness and weakness, aphasia, left gaze preference</td>
</tr>
<tr>
<td>Right MCA</td>
<td>Left face/arm &gt; leg numbness and weakness, left hemispatial neglect, right gaze preference, agraphesia, stereoaognosia</td>
</tr>
<tr>
<td>Left posterior cerebral artery (PCA)</td>
<td>Complete or partial right homonymous hemianopsia, alexia without agraphia; if midbrain involvement, ipsilateral 3rd nerve palsy with mydriasis and contralateral hemiparesis (Weber syndrome)</td>
</tr>
<tr>
<td>Right PCA</td>
<td>Complete or partial left homonymous hemianopsia (same as above if midbrain involvement)</td>
</tr>
<tr>
<td>Superior cerebellar artery (SCA)</td>
<td>Ipsilesional limb and gait ataxia</td>
</tr>
<tr>
<td>Anterior inferior cerebellar artery (AICA)</td>
<td>Vertigo and ipsilesional deafness, possibly also ipsilesional facial weakness and ataxia</td>
</tr>
<tr>
<td>Vertebral/posterior inferior cerebellar artery (PICA)</td>
<td>Ipsilesional limb and gait ataxia; if lateral medullary involvement can have Wallenberg syndrome (see Table 1.4)</td>
</tr>
<tr>
<td>Basilar artery (BA)</td>
<td>Pontine localization with impaired lateral gaze, horizontal diplopia and dysconjugate gaze, nonlocalized hemiparesis, dysarthria</td>
</tr>
</tbody>
</table>

The syndromes above reflect classical neuroanatomy and may vary depending on individual variations in the circle of Willis or collateral vascular supply.
Cortical syndromes

Between large vessel and cardioembolic disease, there are several classic cortical syndromes that when presenting acutely are most often the result of an ischemic stroke. The classic hallmark of a left hemispheric cortical syndrome involves aphasia. Aphasia is defined as an acquired abnormality of language in any form. By and large, aphasia presents as a deficit of verbal language, but truly involves any medium of communication (e.g. reading and writing, or sign language in the hearing impaired). Specific linguistic properties that may be affected by aphasia include volume of speech, vocabulary, cadence, syntax, and phonics. Often, subtle aphasia is difficult to distinguish from encephalopathy and it is important for the bedside clinician to test specific domains of language – fluency, repetition, comprehension, naming, reading, and writing – in order to make the correct diagnosis.

Specific types of aphasia most often encountered in stroke patients (Table 1.2) classically include expressive/motor/nonfluent (Broca’s) and receptive/ sensory/fluent (Wernicke’s) types. Strokes causing expressive aphasia localize to the posterior inferior frontal lobe, or frontal operculum, whereas receptive aphasias commonly originate from lesions in the posterior superior temporal/inferior parietal lobe. Both of these types commonly affect naming and repetition. Broca’s patients are best identified by difficulties with word finding, speech initiation, volume of speech, and in making paraphasic errors (e.g. “hassock” instead of “hammock”). Wernicke’s patients have clearly impaired comprehension with nonsensical speech, but preserved speech volume and cadence. The transcortical aphasias mirror motor and sensory types except in preservation of repetition, due to lack of injury to the arcuate fasciculus linking Broca’s and Wernicke’s areas.

Table 1.2 The aphasias

<table>
<thead>
<tr>
<th>Type</th>
<th>Fluency</th>
<th>Comprehension</th>
<th>Repetition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor/expressive (Broca)</td>
<td>Impaired</td>
<td>Normal</td>
<td>Impaired</td>
</tr>
<tr>
<td>Sensory/receptive (Wernicke)</td>
<td>Normal</td>
<td>Impaired</td>
<td>Impaired</td>
</tr>
<tr>
<td>Conduction</td>
<td>Normal</td>
<td>Normal</td>
<td>Impaired</td>
</tr>
<tr>
<td>Transcortical motor</td>
<td>Impaired</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Transcortical sensory</td>
<td>Normal</td>
<td>Impaired</td>
<td>Normal</td>
</tr>
<tr>
<td>Mixed</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Global</td>
<td>Impaired</td>
<td>Impaired</td>
<td>Impaired</td>
</tr>
</tbody>
</table>

In the bedside evaluation of the stroke patient, differentiating between aphasia subtypes is less relevant than differentiating aphasia from encephalopathy. As most all aphasia emanates from dominant hemispheric injury, commonly middle cerebral artery (MCA) occlusion, one should consider the abrupt onset of aphasia indicative of stroke until proven otherwise.

If aphasia is the hallmark of dominant (left) hemisphere cortical injury, then hemispatial neglect is the hallmark of injury in the nondominant (right) hemisphere. Accordingly, abrupt onset of hemineglect should raise concern for acute stroke by occlusion of the right MCA. Examining the patient with neglect at the bedside is challenging, primarily due to difficulties in teasing out primary contralateral motor weakness and numbness. The most sensitive bedside test for subtle neglect is
double simultaneous stimulation to look for extinction of contralateral sensory modalities. In other words, when presented with bilateral stimuli, the neglectful patient will preferentially identify the ipsilateral stimulus, often in the absence of a primary sensory deficit (see National Institutes of Health Stroke Scale (NIHSS) item 11, in the Appendix, Chapter 9). Extinction may include not only tactile sensation but also other sensory modalities, such as vision or hearing. Motor neglect is typified by preferential use of the ipsilateral limbs when formal confrontational testing reveals no actual hemiparesis. The tactful bedside clinician, when asking the patient to raise both limbs, may observe a delay in or absence of activation of the contralateral side.

Making the evaluation of the neglectful patient more difficult still is the frequent accompaniment of agnosia. These patients may lack awareness of their deficit (anosagnosia) and may seem apathetic to the gravity of their situation. Other nondominant hemispheric phenomena may include stereoagnosia (inability to identify an object by touch), agraphesthesia (deficit of dermal kinesthesia tested by tracing numbers or letters on the palm or finger pad), and aprosodia (analogue of aphasia affecting expression or comprehension of the emotional aspects of language, i.e. pitch, rhythm, intonation). Practically speaking, testing for these more esoteric deficits is not commonly part of the acute stroke evaluation, but may be helpful in confirming suspicion of non-dominant hemispheric ischemia.

**Figure 1.1** The graphical aphasia box.

Agnostic patients presents a unique challenge regarding consent for IV rt-PA as they may refute the need for treatment. One proposed method is to provide a “thought experiment.” Ask the patient hypothetically, “If you were to have a devastating stroke, would you in that instance want to be treated knowing the risks and benefits of tPA as discussed?” An answer in the affirmative places the treating physician on more solid ethical ground in the acute setting [5].

Another cortical syndrome of clinical importance for bedside stroke diagnosis is visual field loss. Simplistically, the abrupt onset of homonymous
hemianopsia is a posterior cerebral artery (PCA) or posterior MCA territory stroke until proven otherwise. Often, visual field cuts present as part of the collage of larger stroke syndromes, but may present in isolation with pure occipital lobe ischemia. Strokes affecting the optic radiations typically cause contralateral quadrantanopsias; temporal lobe ischemia involving the inferior optic radiations (i.e. Meyer’s loop) typically affects the superior visual quadrant, as opposed to parietal lesions affecting the superior optic radiations and the inferior visual quadrant. Clinically, patients often do not recognize visual field loss unless confronted, but historical clues may include bumping into walls or merging into traffic. Rather than recognizing a lateralized deficit in both visual fields, patients more commonly complain of peripheral vision loss in the contralateral eye (easily teased out by confrontational testing at the bedside – see item 3 in the NIHSS). Treating patients with thrombolysis for isolated visual field loss is an individualized decision. While the NIHSS score indicates minor severity in these situations, a visual field deficit may nonetheless be severely disabling, particularly for patients who require good vision for employment or those that already have vision problems at baseline. As in all scenarios, an objective conversation with the stroke patient regarding risk and benefits of therapy will often guide one’s hand.

### Small vessel (lacunar) syndromes
Lacunar strokes include five classical syndromes, with some having multiple possible anatomic localizations (Table 1.3).

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Signs/symptoms</th>
<th>Localization</th>
<th>Vascular supply</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure motor</td>
<td>Contralesional hemiparesis</td>
<td>Posterior limb of internal capsule, corona radiata or basis pontis</td>
<td>Lenticulostriate branches of the MCA or perforating arteries from the basilar artery</td>
</tr>
<tr>
<td>Pure sensory</td>
<td>Contralesional hemisensory loss</td>
<td>Ventroposterolateral nucleus of the thalamus</td>
<td>Lenticulostriate branches of the MCA or small thalamoperforators from the PCA</td>
</tr>
<tr>
<td>Sensorimotor</td>
<td>Contralesional weakness and numbness</td>
<td>Thalamus and adjacent posterior limb of internal capsule</td>
<td>Lenticulostriate branches from the MCA</td>
</tr>
<tr>
<td>Dysarthria–clumsy hand</td>
<td>Slurred speech and (typically fine motor) weakness of contralateral hand</td>
<td>Basis pontis, between rostral third and caudal two thirds</td>
<td>Perforating arteries from the basilar artery</td>
</tr>
<tr>
<td>Ataxia–hemiparesis</td>
<td>Contralesional (mild to moderate) hemiparesis and limb ataxia out of proportion to the degree of weakness</td>
<td>Posterior limb of internal capsule or basis pontis</td>
<td>Lenticulostriate branches of the MCA or perforating arteries from the basilar artery</td>
</tr>
<tr>
<td>Hemiballismus/hemichorea</td>
<td>Contralesional limb flailing or dyskinesias</td>
<td>Subthalamic nucleus</td>
<td>Perforating arteries from anterior choroidal (ICA), PCOM arteries</td>
</tr>
</tbody>
</table>

ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; PCOM, posterior communicating.
Table 1.4 The midbrain and medullary syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Signs/symptoms</th>
<th>Localization</th>
<th>Vascular supply</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weber</td>
<td>Ipsilesional 3rd nerve palsy, contralateral hemiparesis (including the lower face)</td>
<td>Medial midbrain/cerebral peduncle</td>
<td>Deep penetrating artery from PCA (see Table 1.1)</td>
</tr>
<tr>
<td>Benedikt</td>
<td>Ipsilesional 3rd nerve palsy, contralateral involuntary movements (intention tremor, hemichorea, or hemiathetosis)</td>
<td>Ventral midbrain involving red nucleus</td>
<td>Deep penetrating artery from PCA or paramedian penetrating branches of basilar artery</td>
</tr>
<tr>
<td>Nothnagel</td>
<td>Ipsilesional 3rd nerve palsy, contralateral dysmetria, and contralateral limb ataxia</td>
<td>Superior cerebellar peduncle</td>
<td>Deep penetrating artery from PCA</td>
</tr>
<tr>
<td>Wallenburg</td>
<td>Ipsilesional facial and contralateral body hypalgesia and thermoanesthesia, ipsilesional palatal weakness, dysphagia, dysarthria, nystagmus, vertigo, nausea/vomiting, ipsilesional Horner syndrome, skew deviation, singultus</td>
<td>Lateral medulla</td>
<td>PICA (should raise concern for disease in parent vertebral artery)</td>
</tr>
<tr>
<td>Dejerine</td>
<td>Ipsilesional tongue weakness and contralateral hemiparesis +/- contralateral loss of proprioception and vibratory sense</td>
<td>Medial medulla</td>
<td>Vertebral artery or anterior spinal artery</td>
</tr>
</tbody>
</table>

PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery.

- pure motor – contralateral hemiparesis; localizes to posterior limb of internal capsule, corona radiata, or basis pontis (ventral pons); secondary to occlusion of lenticulostriates branches of the MCA or perforating arteries from the basilar
- pure sensory – contralateral hemisensory deficit; localizes to ventroposterolateral nucleus of the thalamus secondary to lenticulostriates or small thalamoperforators from the PCA
- sensorimotor – contralateral paresis and numbness; localizes to thalamus and adjacent posterior limb of internal capsule (thalamocapsular)
- dysarthria – clumsy hand – slurred speech and weakness of contralateral hand usually most evident when writing or performing other fine motor tasks (may also include supranuclear facial weakness, tongue deviation, and dysphagia), localizes to basis pontis between upper third and lower two-thirds
- ataxic hemiparesis – contralateral mild to moderate hemiparesis and limb ataxia out of proportion to the degree of weakness, usually affecting the leg more than the arm, localizes to posterior limb of internal capsule or basis pontis
- there is a rare sixth lacunar syndrome presenting with contralateral hemichorea or hemiballismus from a small infarct in the basal ganglia or subthalamic nucleus.

**CAUTION**

Lacunar strokes typically present with fluctuating symptoms in the acute period. The so-called “capsular warning syndrome” often presents with oscillating sensorimotor deficits over a 24 to 48-hour period representing a small lenticulostriate perforator artery in the process of occlusion. In too many cases, tPA treatment is withheld due to “rapidly improving symptoms” in the hyperacute period only to find the patient with a dense hemiparesis the following morning secondary to completed small vessel stroke.

**Brainstem syndromes**

There are several vertebrobasilar brainstem syndromes that should be recognizable in the acute
stroke setting. These are often caused by occlusion of a small brainstem-penetrating artery stemming from a larger parent vessel, and can therefore be related to either large artery atherosclerosis or small vessel occlusive disease. Less commonly, a microembolus may find its way into one of these perforators, but this is difficult to distinguish without a source of embolus. Named midbrain and medullary syndromes are described in Table 1.4.

Pontine syndromes (see Table 1.1 – basilar territory stroke) are often caused by occlusion of deep or circumferential pontine penetrating branch arteries in the presence of a patent basilar artery. A hallmark of deep pontine infarcts is an abnormality of horizontal gaze and dysarthria. A chief complaint is horizontal diplopia, and presenting signs may include ipsilateral lateral gaze palsy from involvement of the abducens nucleus (CN VI) or as an internuclear ophthalmoplegia (INO) from injury to the medial longitudinal fasciculus that yokes conjugate horizontal gaze – although the latter is consistently seen in paramedian midbrain syndromes as well. Due to proximity of the abducens nucleus to CN VII, these patients may also have a peripheral pattern of facial weakness involving upper and lower facial muscles ipsilateral to the infarct. Involvement of more ventral portions of the pons (i.e. corticospinal and corticopontocerebellar tracts) causes contralateral hemiparesis or ataxia.

**TIPS AND TRICKS**

If a patient presents with neck pain and/or Horner’s syndrome, particularly in young adults, consider cervical artery dissection. Vertebral artery dissection often presents with ipsilesional lateral medullary syndrome and/or cerebellar stroke due to posterior inferior cerebellar artery (PICA) territory infarction. Distal carotid artery dissection may cause lower cranial nerve palsies, but this is a false localizer for brainstem stroke.

**CAUTION**

Be vigilant of the “locked-in” patient; that is a patient who may appear comatose but yet has voluntary blinking or vertical eye movements allowing bedside communication. Locked-in syndrome is caused by bilateral ventral pontine injury with preserved rostral brainstem function including spared level of consciousness from an intact reticular activating system and vertical gaze centers in the midbrain. Similar to top of the basilar syndrome mentioned above, recognizing a devastating pattern of brainstem dysfunction in the acute stroke setting requires immediate evaluation of the basilar artery for possible reperfusion therapy.

**Stroke versus TIA?**

Transient ischemic attacks (TIA) occur in approximately 15% of patients before an eventual stroke, with the highest risk in the first days to weeks following an event [6,7]. While TIAs do not always come to medical attention, their presentation in the acute stroke setting ostensibly complicates the treatment decision in patients who may be exhibiting some improvement. The majority of TIAs resolve in less than 60 minutes whereas the majority of true strokes reach peak deficit in the same time frame. A 2009 scientific statement from the American Heart Association/American Stroke Association discourages the use of traditional time-based definitions of TIA in favor of a tissue-based definition (i.e. the presence or absence of lesions on diffusion-weighted MR imaging) [8]. The fact that 30–50% of TIAs will result in diffusion-weighted abnormalities on brain MRI emphasizes the importance of making a clinical diagnosis in the acute setting. The diagnosis of a TIA requires absolute resolution of symptoms, whereas a persistent deficit should continue to raise concern for a treatable stroke. If a patient returns completely to their neurological baseline (100%), then the clock starts over and any recurrent deficits may be considered a new event (i.e. reopening the treatment window). Evaluation of TIA in the acute stroke setting also requires some assessment of risk. A common practice at US stroke centers is to admit patients following TIA in order to expedite the urgent workup of causative mechanisms, including noninvasive vascular imaging and cardiac evaluation. The ABCD2 score has been established as a validated clinical tool to aid in risk assessment and management decisions [9] (Table 1.5). The AHA/ASA statement referenced above provides the
following recommendation as a possible algorithm in the acute setting:

"It is reasonable to hospitalize patients with TIA if they present within 72 hours of the event and any of the following criteria are present":

a. ABCD2 score of ≥3
b. ABCD2 score of 0 to 2 and uncertainty that diagnostic workup can be completed within 2 days as an outpatient
c. ABCD2 score of 0 to 2 and other evidence that indicates the patient’s event was caused by focal ischemia.

Stroke mimics

Of the many judgments required of the stroke physician at the bedside during an emergency, perhaps the most difficult is consideration of the stroke mimic. As treatment with rt-PA clearly is not without risk it is important that the physician be able to rapidly differentiate a stroke mimic from symptoms due to retinal, hemispheric, or brainstem ischemia. The following paragraphs highlight frequently encountered stroke mimics and how to more reliably differentiate them from ischemic stroke in the bedside evaluation.

Following a seizure, postictal focal neurological deficit can appear identical to any cortical stroke syndrome, and without a reliable history or eyewitness can be nearly impossible to diagnose prospectively. One would hope that the seizure patient would be able to provide a telling history but this often is not the case, particularly in encephalopathic or aphasic patients when the ictal event is un witnessed. The most commonly encountered postictal phenomenon is Todd’s paralysis (postictal hemiparesis), but the bedside physician should be aware that almost any focal cortical neurological deficit can be witnessed following a seizure depending on the anatomic location of the seizure focus. Examples include postictal aphasia, sensory disturbance, and neglect. While seizure at the outset of symptoms is a relative contraindication to rt-PA, it should be noted that focal seizures can often herald ischemic stroke onset, particularly of cardioembolic origin. In cases of high suspicion for stroke, attention should be made to the bedside exam and head CT for diagnostic confirmation before ruling out treatment options.

Another common mimic that can be difficult to diagnose is migraine with aura. The migraine patient, of course, typically will have an associated headache most often following the onset of focal neurological symptoms. However, this is not always the case. Older individuals, in particular, are prone to migraine equivalents without head pain, making the diagnosis even more difficult as this population is typically also at a higher risk for stroke. Like seizures, migraine equivalents can mimic almost any focal cortical neurological deficit due to the spreading cortical depression that is characteristic of migraine pathology. A history of migraine, as well as the presence of commonly associated symptoms of nausea, anorexia, photophobia, phonophobia, and positive visual phenomenon, can be helpful. Other clues include a temporal “marching” quality of symptoms (i.e. from face to arm to leg) and positive symptoms such as parasthesias. However, it should be emphasized that the diagnosis of migraine in the acute stroke patient, particularly in persons with legitimate vascular risk factors, remains a diagnosis of exclusion. Hemorrhagic

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Table 1.5 The ABCD2 score

<table>
<thead>
<tr>
<th>Age</th>
<th>Blood pressure ≥140/90 mmHg</th>
<th>Clinical features Other than below 0 points</th>
<th>Speech disturbance without weakness 1 point</th>
<th>Unilateral weakness 2 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Present</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>&lt;10 minutes</td>
<td>0 points</td>
<td>1 point</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10–59 minutes</td>
<td>1 point</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥60 minutes</td>
<td>2 points</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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★ TIPS AND TRICKS

Gaze preference may help differentiate seizure versus stroke – in a large MCA stroke, eyes will deviate towards the lesion, i.e. away from the side of paralysis. In an ongoing seizure, eyes will deviate away from the ictus, i.e. towards the side of focal motor tonic–clonic activity. Gaze may reverse preference in the postictal state, looking away from Todd’s paralysis.
strokes and some less common causes of ischemic stroke, such as reversible cerebral vasoconstriction syndrome and carotid dissection, may be associated with acute headache at the time of the event.

Metabolic derangements that may mimic stroke include hyper- or hypoglycemia, electrolyte disturbances, or infection. It is widely held that any metabolic stress on the body can cause “stroke reactivation” or “anamnestic syndrome.” In this case, symptoms of a prior stroke from which a patient has recovered can re-emerge as the metabolic stress on the brain increases. A history of identical symptoms during a prior ischemic event or evidence of chronic infarction in a relevant vascular territory on noncontrast head CT can help make this diagnosis. Generally, neurological symptoms improve in parallel with correction of infectious/metabolic derangement.

Multiple sclerosis (MS) may mimic almost any other neurological disorder, including stroke. MS tends to present in middle-aged women, sometimes with history of other autoimmunne disease. MS flares tend to have a “crescendo–decrescendo” character and if a careful history is taken, symptoms rarely are at their most severe at onset, as is the case in stroke. Isolated acute demyelinating lesions may also show restricted diffusion on brain MRI, often difficult to distinguish from acute infarct without corroborating history and exam.

A mass lesion may mimic stroke but generally will present with headache, which is classically positional (worse with lying down or with Valsalva maneuvers), and nausea/vomiting. Symptoms in this case are likely to be gradual in onset; however, hemorrhagic metastases can produce acute neurological changes and seizure as well.

Peripheral vertigo may be very difficult to distinguish from ischemia in the posterior circulation. Helpful characteristics in identifying central vertigo are vertical nystagmus, nystagmus that changes direction with change in gaze, and neighborhood brainstem signs and symptoms (e.g. diplopia, dysphagia, dysarthria). A positive Dix–Hallpike test or head thrust maneuver may suggest a peripheral etiology, though, ultimately, a patient with a high-risk vascular profile and acute vertigo must immediately raise the clinician’s concern for stroke. Notably, medial branch PICA territory infarctions in midline cerebellar structures often present with isolated acute vestibular syndrome.

Occasionally, isolated limb weakness or numbness is caused by a peripheral lesion (e.g. foot drop from peroneal compression, arm weakness from cervical disc disease) and will mimic stroke. Peripheral causes of weakness or sensory disturbance are usually excluded by a careful examination. A practical example includes the “Saturday night” radial nerve palsy causing wrist drop that may mimic cortical hand syndrome from a stroke in the lateral precentral gyrus or “hand knob.” In peripheral wrist drop, supporting the wrist will reveal intact strength of intrinsic hand muscles as opposed to a cortical hand syndrome.

Probably the most common stroke mimics reflect somatization or conversion disorder. These patients are especially difficult to diagnose, commonly presenting with hemiparesis/hemiplegia, unilateral sensory disturbance, or speech arrest. Functional aphasia is generally relatively easy to detect by an experienced examiner, as these patients can present with stuttering speech rather than lack of fluency, or will be slow to respond to questions without having any legitimate word-finding difficulty or comprehensive errors.

| ★ TIPS AND TRICKS |
|____________________|
| True expressive aphasia should also involve agraphia; the inability to speak with preserved ability to communicate through writing is characteristically not consistent with physiological aphasia. |

Functional hemiparesis may be challenging to distinguish, but there are some relatively straightforward bedside maneuvers that can aid in the diagnosis. Examples include the Hoover sign, observation of upper extremity drift without pronation, and effort-dependent and break-away weakness. Subjective numbness in a nonanatomic pattern is another clue. For example, inability to detect vibration over the left side of the frontal bone while vibratory sense remains intact over the right is not a physiological deficit. The subjectivity of sensory symptoms makes some vascular neurologists hesitant to offer treatment in these cases, though it should be pointed out that thalamic stroke can present with a true sensory deficit.
SCIENCE REVISITED

In a review of 512 consecutive cases treated with IV rt-PA within 3 hours of symptom onset, 21% were found not to have an infarct on follow-up imaging. The most common stroke mimics encountered included seizure, complicated migraine, and somatization. More importantly, there were no instances of symptomatic intracerebral hemorrhage, emphasizing the minimal risk of treatment in this group [10]. If suspicion for ischemic stroke exists, one should not withhold treatment simply for fear of a mimic.

The history – guessing the age of a stroke and more

Once the neurologist suspects that an acute stroke is the cause of the patient’s symptoms, the next immediate question to be answered is whether that patient is appropriate for treatment. The critical factor in this determination is frequently the most difficult – the exact time when the patient was last known well. This seems fairly straightforward, but in practice it can be challenging. The physician is often very clearly told when the patient was first known unwell but this point is somewhat irrelevant. For consideration of treatment within recommended time windows, the clock starts when the patient was last known to be symptom free. A substantial proportion of patients are alone when their stroke symptoms begin, and if they are unable to provide a clear, cogent history the physician must obtain that detail of the history from whomever saw them last. This is important particularly in patients who awaken with their symptoms.

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A number of published stroke registries in the 1970s–1980s found an early to midmorning predominance in onset of ischemic stroke, potentially coinciding with diurnal peaks in blood pressure and cortisol. Unfortunately, many stroke patients wake up with their symptoms, making any determination of a time of onset difficult [11]. Research is underway to determine the safety and efficacy of treating wakeup stroke with thrombolysis.

Unless the patient awoke at some point during the night and was clearly asymptomatic (e.g. able to ambulate to the bathroom or speak to their spouse, but now aphasic and hemiparetic), the window for treatment, by definition, would begin when they were last known well – in this case, the evening before, prior to going asleep.

TIPS AND TRICKS

Witnesses do not often volunteer this information, so it is important to investigate such things as nighttime awakenings, possible phone conversations (check their mobile phone for recent calls), evidence of normal activity such as shopping receipts, or potential witnesses who regularly interact with a patient found down. Searching a purse or wallet from Jane or John Doe stroke patients may provide crucial clues or contact information that could lead to treatment.

Once the time the patient was last known well is firmly established, there are several other key pieces of basic medical information that should be attained on arrival for evaluation of the acute stroke patient. The patient’s blood pressure and blood sugar are important, as are the ranges of each that are considered appropriate for treatment with IV rt-PA. A blood pressure of more than 185/110 mmHg that is not correctable is considered an absolute contraindication to treatment; considering this early in the acute evaluation will save time when the rt-PA is ready. Serum glucose of less than 50 mg/dL or greater than 400 mg/dL is also a contraindication, as this may suggest the presence of a mimic. If possible to attain, a brief past medical history is essential. Particularly important is the consideration of a potential stroke patient’s vascular risk profile: history of hypertension, diabetes, hyperlipidemia, smoking, atrial fibrillation, and of course, prior stroke or TIA. While clearly none of the above is required to diagnose stroke and the absence of risk factors should not preclude treatment if suspicion for stroke is high, weighing a patient’s risk can help tip the scales when making a swift judgment about whether or not to administer rt-PA in an unclear case. A quick review of a patient’s medication list is helpful. Not only can a medication list give clues as to prior medical history, but also the presence of
warfarin or other anticoagulation adds a significant factor to be weighed in the ultimate decision to treat (more below in the laboratory section).

**Rapid examination of the acute stroke patient**

After obtaining a clear understanding of the initial presentation with particular attention to when the patient was last known well, a focused medical history, and a brief review of medications, the physician should move to the focused physical examination. In the rapid evaluation of acute stroke, this exam is essentially the NIH stroke scale (see Chapter 9 Appendix). This 11-item examination was designed as a research tool to quickly and consistently measure stroke severity; however, since the report of the NINDS tPA study, it has become mainstream clinical practice in the acute stroke setting. The NIHSS contains selected elements commonly affected in acute stroke syndromes including evaluation of mental status, cranial nerves, visuospatial, motor, sensory, and cerebellar function and can be performed by the experienced examiner in roughly 5 to 10 minutes. By the completion of the NIHSS, the physician should have a reasonable idea of whether the patient is having a stroke, the severity of the deficit, and the localization of the lesion in the nervous system. The scale is designed such that the higher the score, the more severe the neurological impairment, with scores ranging from 0 to 42. Minor strokes, such as those caused by small emboli, are generally considered in the range of 0–4 points, with large artery strokes caused by proximal vascular occlusions producing symptoms commonly exceeding 10 points.

While the NIHSS is a rapid and fairly consistent screening tool, one should be aware of its limitations. For example, the scale will differentially rate ischemic lesions of identical volume depending on the hemispheric location. A complete, proximal left middle cerebral artery occlusion will generate an NIHSS score in the 22–25 range, whereas the same proximal occlusion in the right MCA territory will give a score closer to 15. This is due to the fact that aphasias is given more weight than neglect in the scoring paradigm. If the physician is concerned about a lesion in the nondominant parietal lobe, an insult that is commonly unrecognized as a stroke, evaluating the patient for agraphesthesia and stereognosis is not only appropriate but may well be more helpful than any part of the NIHSS. There are some strokes that do not register any points on the scale. Examples are the embolic stroke affecting the portion of the motor strip that controls hand or finger movements, or the midline cerebellar stroke affecting gait but not limb ataxia. Small lacunar strokes in the posterior fossa can cause isolated vertigo that can be extremely disabling but could still register no score on the NIHSS. A low score (even 0) on the NIHSS should not, by default, defer the physician from considering treatment. While the NIHSS is a validated, rapid way to evaluate the function of the nervous system, it originated as a measure of stroke severity for clinical trials and is not meant to be a substitute for a thorough neurological exam.

Beyond the NIHSS and other focused neurological examination, there are a number of general physical findings that are useful in evaluation of the acute stroke patient. Vital signs, especially blood pressure, are of particular interest. Not only does hypertension at presentation convey an increased risk of stroke but, as was previously mentioned, the administration of rt-PA requires blood pressure of less than 185/110 mmHg. Complicating matters further is that rapid lowering of blood pressure in the acute stroke patient can actually be detrimental due to its deleterious effects on cerebral perfusion.

Auscultation of cardiac and carotid sounds can be beneficial in some cases, as can palpation of peripheral pulses. An irregularly irregular cardiac rhythm, for example, may indicate atrial fibrillation, which may provide a substrate for cardioembolism. A patient with stroke symptoms, chest pain, and asymmetric radial pulses may have a thoracic aortic dissection or aneurysm, which is a vascular surgical emergency and should prompt additional vascular imaging of the chest and neck in addition to head CT. Pupillary asymmetry can be another helpful observation, though not a formal part of the NIHSS. In a young patient presenting with neck pain and stroke symptoms, miosis and partial ptosis are signs of Horner’s syndrome, often associated with carotid dissection due to disruption of the ascending cervical sympathetic chain. Lastly, while also not a part of the NIHSS, eliciting muscle stretch reflexes for upper motor signs (i.e. hyperreflexia, clonus, Babinski sign) may be useful in distinguishing central from peripheral causes of weakness (keeping in mind that in the acute setting, the stroke patient may well present with normoactive reflexes).
Diagnostic data

The all important head CT

After collection of a brief history and execution of a focused, screening neurological examination, the physician should have an idea regarding the likelihood that the patient is to be offered emergent treatment for his/her symptoms. The next step is to obtain a stat noncontrast CT of the head. It is obligate that this study be obtained prior to the delivery of any treatment for acute stroke in order to rule out intracerebral hemorrhage (ICH).

While acute ischemic stroke and ICH may have virtually the same clinical presentation, some historical features can be a clue to the latter such as more prominent headache, uncontrolled hypertension, more abrupt signs of increased intracranial pressure, or a known coagulopathy. Nevertheless, these entities are clinically similar enough to warrant CT imaging in all cases where diagnostic differentiation is necessary. Current AHA/ASA and JCAHO guidelines recommend an interval of no more than 20 minutes between patient arrival and initiation of head CT. While it is not required that all physicians treating acute stroke be neuroradiological experts, it is beneficial to appreciate certain corroborative signs of ischemic stroke on the non-contrast head CT. The most commonly observed radiological signature of large vessel occlusions is the hyperdense artery sign. For MCA occlusions, this will appear as a dense proximal M1 segment at the base of the brain ipsilateral to a clinical hemispheric syndrome.

Tips and Tricks

Acute hemorrhage is hyperdense on head CT; other hyperdense findings on CT include calcification (choroid plexus, pineal gland, basal ganglia), intravenous contrast, bone, and metallic materials such as endovascular aneurysm coils or shrapnel. Hyperdensity can be measured in Hounsfield units and can be used by the experienced neuroradiologist to differentiate acute hemorrhage from calcifications.

Dehydration or calcific atherosclerosis may cause arteries to look hyperdense on CT; the key is to compare the dense artery with the contralateral side. If both sides are “dense,” consider one of the above radiological mimics and whether the imaging fits with the clinical presentation.

While the dense artery sign is most often observed when there is acute thrombus in the proximal MCA, it is also a diagnostic sign of basilar artery occlusion. The latter, while easily recognized by the trained radiological eye, is frequently missed by the bedside examiner due to the often less-clear picture of brainstem ischemia.

Dehydration or calcific atherosclerosis may cause arteries to look hyperdense on CT; the key is to compare the dense artery with the contralateral side. If both sides are “dense,” consider one of the above radiological mimics and whether the imaging fits with the clinical presentation.

In the comatose patient being evaluated for acute stroke, pay close attention for the dense basilar artery sign indicating “top of the basilar” or “locked-in” syndrome. These are devastating ischemic events necessitating immediate reperfusion efforts.

Another early ischemic change appreciated on head CT is the loss of the “insular ribbon,” or the loss of gray–white differentiation in the cortex secondary to ischemia from MCA occlusion. This is best appreciated in contrast to the opposite hemisphere with normal perfusion. This is particularly important when trying to appreciate the size or age of an infarct. When the time of stroke onset is unclear, a marked hypodensity may indicate an infarct is older than a few hours. Early ischemic changes encompassing greater than one-third the MCA territory likely represents sizable infarct of great severity, and may be a poor prognostic factor for late attempts at reperfusion.

Head positioning within the CT scanner should be accounted for; a head positioned askew in the CT gantry can result in the false appearance of cortical asymmetries.
Though all of these signs can be seen in the acute stroke evaluation, the absence of clear evidence of stroke on the CT scan should not discourage treatment - in fact, except in those cases mentioned above, the head CT in the acute stroke setting may well be entirely unremarkable.

**Laboratory and ancillary studies**

While the physician is obtaining a history, performing a neurological examination, and reviewing the head CT, blood should have been obtained from the patient and been delivered to the laboratory with results pending. As emphasis, it is of vital importance that blood be collected and sent to the lab shortly after the patient arrives to the emergency department and certainly before travel to the imaging suite. This is important because of the potential need to review laboratory results prior to administration of thrombolytic. Blood glucose must be obtained prior to treating with IV tPA. Many patients can be treated prior to final lab results if there is no clinical reason to anticipate an abnormality. During the typical stroke alert, complete blood count, basic metabolic panel, and coagulation profile should be sent at a minimum. If a patient reports warfarin as a home medication, the physician *must* know the INR prior to initiating treatment with rt-PA. In the NINDS tPA trial, any patient was excluded for rt-PA if warfarin had been taken in the previous 24 hours. However, the FDA stipulated excluding treatment only for an INR >1.7. This criterion varies across centers and ultimately it falls on the physician to make a best judgment of risk over benefit, and hence the reason a quick but thorough review of past medical history and the patient’s home medications is crucial in the early stages of evaluation. The most likely reason a patient with atrial fibrillation on warfarin presents with acute stroke is secondary to a subtherapeutic INR. Other important data to review before treatment with IV rt-PA are PTT (in cases where heparin has been used in the last 24 hours) and a platelet count >100,000/μL.

Additionally, the recent approval and growing usage of nonwarfarin anticoagulants for stroke prevention in atrial fibrillation - including the direct thrombin inhibitor, dabigatran, and factor Xa inhibitor, rivaroxaban - may not reveal an abnormal coagulation profile in all cases. Therefore, it is vital to know the current medications for stroke patients with atrial fibrillation being considered for tPA, independent of laboratory data.

Along with phlebotomy, establishing intravenous access immediately upon patient arrival and prior to travel to CT is also crucial, both so that the rt-PA bolus may be administered immediately upon determination of its indication and in order to deliver intravenous contrast in the event that angiographic imaging is required. This is not only of clinical import, but also may be an obstacle to recommended door-to-CT time, particularly in older patients with difficult venous access.

The final piece of data that should not be forgotten during the acute stroke evaluation is the electrocardiogram (ECG). Acute stroke and myocardial infarction often coincide and the latter should not be overlooked when focused on the management of the former. Acute coronary syndrome can also cause acute neurological deficits, generally as a result of cerebral hypoperfusion that is unmasked during an episode of relative hypotension. Many stroke centers include serum troponin among the laboratory studies that are routinely sent during the initial evaluation. In the case of acute myocardial infarction presenting with neurological deficit, rapid support of the cardiovascular system is vital. In the unstable patient, addressing cardiorespiratory status is the foremost priority regardless of the neurological condition.

**Biomarkers in acute stroke diagnosis?**

In addition to advances in neuroimaging, avid research is underway to establish a serum biomarker for acute stroke diagnosis, the so-called “stroke troponin.” Numerous individual proteins and protein panels have been studied, including such markers as N-methyl D-aspartate (NMDA) receptor antibodies, metalloproteinases, and von Willibrand’s...
factor, but lack appropriate specificity to distinguish ischemic stroke from other brain injury or vascular disease [12]. Gene expression profiles offer the promise of greater specificity. In 2006, Tang and colleagues demonstrated that RNA transcribed by serum leukocytes could derive a gene expression profile distinguishing patients with acute ischemic stroke from normal controls with sensitivity 89% and specificity 100%, and later validated this 18-gene panel in a larger cohort achieving sensitivity/specificity of 93/95%. A separate analysis by Barr et al., using a different microarray chip, reported similar results with a nine-gene panel deriving five of the same genes [12]. The promise of RNA expression analysis has been further demonstrated in distinguishing ischemic stroke subtypes in the acute setting, which might help tailor diagnostic and treatment pathways. While this area of research is exciting, external validation in larger cohorts is required before translation to clinical care can be reached. Beyond serving as a tool in ischemic stroke diagnosis, other potential applications of serum biomarkers in the acute stroke setting include prediction of ischemic penumbra, estimation of infarct volume, and correlation to eventual outcome.

The decision to treat
After diagnosis of acute stroke, appraisal of radiographic and laboratory data, and careful review of exclusion criteria for rt-PA, the physician should be prepared to offer treatment. In general, IV rt-PA is considered an emergent therapy and patient consent is not mandatorily required although individual hospitals may apply this exception to the requirement for informed consent differently. Use of presumed consent in emergency situations is particularly relevant for aphasic or encephalopathic stroke patients where communication is challenging and the need for treatment is imminent. However, in most situations a discussion with the patient or their family prior to treatment is prudent and requires the physician to be knowledgeable of the risks and benefits of therapy – discussed in detail in the chapter on stroke therapeutics. The points to be covered are relatively straightforward, but time is a major concern so balance in addressing the important details without dwelling on minutiae is important. By this point, the physician should already have ordered IV rt-PA from the pharmacy and be ready to retrieve it once the decision to treat is made. Additionally, communication with the nursing staff during this time is essential for rapid administration of treatment: IV access should be ensured, an infusion pump should be at the bedside, and close BP monitoring should meet parameters less than 185/110 mmHg (i.e. treat with IV labetalol pushes, nicardipine drip as needed).

The last thing that should be done prior to pushing the IV rt-PA bolus is a final pretreatment assessment of the NIHSS. This can be brief and focused, but the examiner needs to ensure the persistence and consistency of the deficit. While rapidly improving or minor symptoms are a relative contraindication to treatment in the listed exclusion criteria, this should be considered in the context of each given case. As aforementioned, the physician and patient can consider the perceived disability if the deficits prior to treatment were to persist with no further improvement. Stroke symptoms (particularly in small vessel occlusions) can often fluctuate, so the bedside exam most proximate to the moment of treatment is ultimately the most reliable. Again, one should not withhold treatment for minor improvements in the neurological exam, particularly when the patient is not returning to baseline.

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Treatment of acute ischemic stroke is time-dependent, and receiving IV tPA is the most important factor associated with favorable outcomes other than the severity of the stroke itself. Pooled analysis from the NINDS rt-PA, ECASS, and ATLANTIS clinical stroke trials reveal the odds of a favorable outcome decrease with every extended minute from onset to treatment with tPA [13]. These minutes of delay equate to worse outcomes in stroke manifesting as increased long-term disability and death. The AHA/ASA’s GWTG program recommends door-to-needle (i.e. IV tPA) time of ≤60 minutes, a goal achieved in less than one-third of all ischemic stroke patients treated in the US [3]. Yet, the concept of “ultraearly” stroke treatment has been realized by a group from the Helsinki University Central Hospital who published a simple protocol in 2012 achieving median door-to-needle times of 20 minutes [14].
Conclusion

Clearly, this chapter cannot fully encompass the spectrum of ideas, opinions, and evidence that guide the evaluation of the acute stroke patient, nor does it highlight the entirety of hard work and ongoing research dedicated to improving the current provision of acute stroke care. Nevertheless, the principles are universal: acute brain ischemia is the downstream result of often-chronic disease where physicians and provider teams have the ability to most immediately impact a stroke patient’s life and future abilities. The ultimate goal of any acute stroke protocol in the current age is to rapidly establish the time of symptom onset, make an accurate bedside diagnosis, and administer reperfusion therapy to eligible patients; yet it is the providers and patients themselves that enable the achievement of quality and effective care and all together should continue to herald the charge, “time is brain.”

Selected bibliography

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