8 Hyperacute Ischemic Stroke in Adults: Evidence-Based Emergency Imaging

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Key Points

- Noncontrast head CT should be performed expeditiously in all patients with hyperacute ischemic stroke to evaluate for intracranial hemorrhage (ICH) [Strong Evidence]. Magnetic resonance imaging (MRI) is equivalent to CT in the detection of intracranial hemorrhage for patients <6 h from onset [Strong Evidence] but typically takes longer to perform, potentially delaying time-sensitive therapies which can worsen outcomes [Strong Evidence].
- Magnetic resonance diffusion-weighted imaging (DWI) is superior to CT for the detection of ischemic stroke within the first 24 h of symptom onset [Strong Evidence]. However, MRI may confirm a clinical diagnosis of ischemic stroke *without* influencing outcomes and potentially delaying time-sensitive therapies, though may remain useful when the clinical diagnosis is unclear [Limited Evidence]. Patients at high risk for hemorrhagic conversion and poor outcome regardless of intravenous thrombolysis can be predicted with noncontrast head CT and MRI [Moderate Evidence], but such high-risk patients still may marginally benefit from intravenous thrombolysis despite overall increased risk of worse outcomes [Limited Evidence].
- CT angiography (CTA) should be performed expeditiously in hyperacute stroke patients who are potential candidates for endovascular thrombectomy (EVT) to evaluate for large vessel occlusion (LVO) [Strong Evidence]. CTA is generally safe and can be performed without first evaluating renal function [Moderate Evidence].
- The net benefit of EVT in severe ischemic strokes may be modestly predicted by determining the size of an ischemic core, with CT and Alberta Stroke Program Early CT (ASPECTS) scoring [Moderate Evidence] CT perfusion [Moderate Evidence] or MRI and DWI [Moderate Evidence]. However, the interrater variability of ASPECTS scoring and time

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delays arising from MRI or advanced imaging need to be weighed carefully against the utility of avoiding EVT.

- Identification of "salvageable tissue" by either identifying a "penumbra" or collateral flow with advanced imaging techniques predicts outcomes in hyperacute stroke patients after intravenous thrombolysis and EVT [Strong Evidence] but does so for untreated patients also [Strong Evidence]. Selection of patients based on the presence of a penumbra with perfusion imaging or collateral flow with multiphase CTA identifies patients more likely to benefit from EVT within 6 h though might exclude patients who could have benefited from EVT in this time window [Moderate Evidence]. However, beyond 6 h CT perfusion, imaging and multiphase CTA may help select patients that could still benefit from EVT [Strong Evidence, pending publication of trial results at the time of this writing].
- Time to intravenous thrombolysis and EVT highly influences outcomes [Strong Evidence], and reducing the time of imaging and interpretation expedites treatment delivery to hyperacute stroke patients [Strong Evidence]. Improving systems of stroke care, including imaging in the hyperacute setting, is thus likely to improve neurological outcomes.

Definitions and Pathophysiology

Stroke is a clinical term that refers to an acute neurological deficit arising from disruption of focal blood supply to the brain [1]. Stroke may be due to an occlusion or stenosis of an artery or arteries (ischemic stroke), rupture of an artery leading to hemorrhage in or around the brain (intracranial hemorrhage), or from occlusion of a cerebral vein or dural sinus. The vast majority of strokes are ischemic (~85%) [2], and etiologies are protean and include arterioarterial emboli from large vessel atherosclerosis, small-vessel atherosclerosis, cardiogenic or other systemic emboli, and arterial dissection, among other more uncommon etiologies.

This chapter focuses on the imaging of ischemic stroke patients within the first several hours after stroke onset, i.e., *hyperacute* ischemic stroke. We do not use this term to refer to a specific time interval after stroke onset but rather for patients who stand to benefit from emergently applied therapies including intravenous thrombolysis or EVT. Thus, the time interval from stroke onset might be as short as 4.5 h for patients who are not candidates for EVT to as long as 24 h for imaging-selected patients. Imaging may have utility beyond this hyperacute period, for example, in identifying the etiology of a stroke or predicting the need for hemicraniectomy in a patient with "malignant" ischemic stroke. However, these issues are typically dealt with after the patient has left the Emergency Department, which is beyond the scope of this chapter.

Epidemiology

It is estimated that approximately 795,000 ischemic strokes occur in the United States annually [3]. In the United States, stroke is now the fifth leading cause of death and the second leading cause of adult disability, down from the third and first leading causes, respectively, due to improvements in stroke prevention and treatment, yet remains the second leading cause of death worldwide [4, 5]. In the emergency room, cerebrovascular disease accounts for over 700,000 visits (0.5% of all Emergency Department visits) in the United States annually.

Costs to Society

The estimated direct and indirect costs of stroke in the United States in 2010 were 74 billion dollars [6]. Acute inpatient hospitalization accounts for 70% of the first-year costs after stroke, and diagnostic testing represents approximately 20% of this cost.

Goals of Imaging

Here, we take the approach that imaging and its interpretation should be driven solely by its ability to improve neurological outcomes, which inherently relies on its ability to help select patients for *proven* therapies. In the hyperacute setting, the principal goals of imaging are to (1) identify candidacy for intravenous thrombolysis and (2) identify candidacy for EVT. While imaging may have a role in predicting outcomes without or with treatment, it is important to note that the goal may include selecting patients that might benefit from therapy even when prognosis is generally (though not universally) poor. For example, patients above the age of 80 are likely to have worse outcomes after ischemic stroke than those below the age of 80 but receive the same benefit from intravenous thrombolysis [7] and even further benefit from EVT regardless of their age [8, 9].

It is also important to note that the incremental benefit of an imaging modality must be weighed against the additional time required to obtain this imaging. For every 15 min saved in administering intravenous alteplase, nearly 1 month of disability-free life is gained, and the number needed to treat to achieve good outcomes significantly improves [10]. The value of providing endovascular treatment more quickly has an even larger benefit [11, 12]. The additional time added by an imaging modality must thus account for patient transfer, preparation, scan time, post-processing, image transfer, and interpretation. Conversely, minimizing these times is likely to improve the benefit of the imaging modality in improving neurological outcomes.

Methodology

The evidence and literature cited here were identified through several search strategies including keyword searches via PubMed and Google Scholar, references contained within review articles and other key references, and personal collection of key literature on stroke imaging, updated to the time of this writing (March 2017).

Discussion of Issues

Should This Patient Receive Intravenous Thrombolysis?

In 1995, the Food and Drug Administration approved intravenous tissue plasminogen activator (IV-tPA) for the treatment of acute ischemic stroke after two randomized controlled trials (RCT) demonstrated its efficacy in improving neurological disability at 3 months when intravenously administered within 3 h of stroke onset [13]. A subsequent RCT showed that IV-tPA improved neurological outcomes in patients presenting within 4.5 h of stroke onset [14]. After IV-tPA an additional one in ten patients remains independent in their daily activities, and one in three to six patients, depending on time to treatment, shows some improvement in their disability, as compared to those treated with a placebo [15].

Despite the strong evidence supporting this treatment, only a minority of potentially eligible patients receives IV-tPA, largely due to patients arriving beyond the 4.5 h time window [16]. Several other factors limit candidacy for IV-tPA, particularly those that herald an increased risk for hemorrhagic complication, which include the presence of acute intracranial hemorrhage and a particularly large ischemic stroke more likely to hemorrhage. Head imaging thus plays a critical role in this evaluation (Question 1.1).

It may seem intuitive to use imaging to confirm the diagnosis of ischemic stroke prior to IV-tPA (Question 1.2). However, treatment of stroke mimics with intravenous thrombolysis has been found to be safe [17–19] [Strong Evidence], and the desire to improve diagnostic certainty of stroke may introduce delays in administering treatment, which is known to worsen outcomes [15, 20, 21] [Strong Evidence]. Establishing the diagnosis of acute ischemic stroke with imaging may yet continue to have a role in patients with unknown time of symptom onset or in patients who are unlikely to have a stroke but could receive thrombolysis if proven otherwise.

A third concern is whether treatment with IV-tPA in a patient with a particularly large ischemic stroke will lead to hemorrhagic conversion

and thereby worsened outcomes (Question 1.3). No such criteria were used in the initial National Institute of Neurological Disorders and Stroke (NINDS) trials demonstrating efficacy of IV-tPA in the first 3 h after symptom onset [13]; subsequent subgroup analyses have shown that while hemorrhagic conversion and poor outcomes increase in patients with very large ischemic strokes, there is persistent benefit for IV-tPA in these patients [7] [Moderate Evidence]. On the other hand, the European Cooperative Acute Stroke Study (ECASS) III trial, which demonstrated efficacy of IV-tPA in the 3–4.5 h window, specifically excluded patients with a large middle cerebral artery (MCA) stroke (defined as greater than 1/3 of the MCA territory) [14]. Thus, determining the presence of a large stroke that is likely to hemorrhage remains standard practice for patients being treated within the 3–4.5 h time window, though no study has proven that excluding such patients affects outcomes [Limited Evidence].

Does This Patient Have an Acute Intracranial Hemorrhage?

Summary of Evidence Noncontrast head CT (NHCT) is widely accepted as the gold standard for detection of acute intracranial hemorrhage [Moderate Evidence] and is the modality of choice for exclusion of intracranial hemorrhage in evaluation for thrombolytic candidacy, based on its successful use in several RCTs [Strong Evidence]. MRI can replace NHCT, as it is nearly as sensitive in detecting acute intracranial hemorrhage [Strong Evidence]. However, when compared to NHCT, MRI may cause a delay in treatment [Moderate Evidence], which is known to worsen outcomes [Strong Evidence]. No other method, imaging based or otherwise, has demonstrated superior or equivalent efficacy to NHCT.

Supporting Evidence

(i) *Noncontrast head CT (NHCT)* Acute hemorrhage appears hyperdense on NHCT for several days due to the high concentration of hemoglobin in compressed blood and then becomes progressively isodense and then hypodense over a period of weeks to months. Hyperacute hemorrhage can rarely be isodense in the acute period in severely anemic patients [22]. No rigorous prospective study has been performed to validate the sensitivity and specificity of noncontrast head CT in detecting intracranial hemorrhage (ICH). In an early single autopsy series of 79 patients, CT did not detect 4 out of 17 patients with ICH—all brainstem hemorrhages [23]. However, this study was performed using a first-generation CT scanner, and experience with NHCT was just beginning. More recent studies evaluate the role of NHCT in diagnosing subarachnoid hemorrhage as compared to cerebrospinal fluid analysis. The overall sensitivity of NHCT for subarachnoid hemorrhage is 91–92% but is time dependent such that the sensitivity is nearly 100% within the first 6 h [24–26]. RCTs demonstrating the efficacy of IV-tPA nearly always used NHCT to exclude patients with ICH [13, 14]; in these trials, subsequent hemorrhage typically occurred in the setting of very large ischemic strokes suggesting that an underlying missed ICH was very unlikely to account for subsequent hemorrhagic complication. Thus, NHCT is widely accepted as the gold standard for detection of acute ICH, particularly when evaluating patients for thrombolytic candidacy.

(ii) *Magnetic resonance imaging (MRI)* The appearance and identification of ICH on MRI depend on the age and location of the hemorrhage, the strength of the magnetic field, and the type of MR sequence [27]. As the hematoma ages, oxyhemoglobin breaks down sequentially into several paramagnetic products: first deoxyhemoglobin, then methemoglobin, and finally hemosiderin. Iron exposed to surrounding water molecules in the form of deoxyhemoglobin creates signal loss on susceptibility-weighted and T2-weighted (T2 W) sequences [28, 29]. Thus, the earliest detection of hemorrhage depends on the conversion of oxyhemoglobin to deoxyhemoglobin which was believed to occur after the first 12–24 h [27].

However, this early assumption had been questioned with reports of ICH detected by MRI within 6 h and as early as 23 min from symptom onset [30, 31].

More recently, studies have assessed MRI (diffusion-, T2-, and T2*-weighted images) for the evaluation of ICH within 6 h of onset. One study evaluated 62 ICH patients and 62 nonhemorrhagic stroke control patients, with three experienced readers (two stroke neurologists and one neuroradiologist) utilizing CT as the reference standard [32]. The readers, blinded to clinical and CT results, identified all acute hemorrhages on MRI yielding 100% sensitivity and specificity compared to CT. Subsequently, prospective studies compared MRI and CT for detection of ICH. In the first study, 4 of 25 acute ICH patients were not identified by MRI including three cases in which "acute" ICH was classified as "chronic" and one case of subarachnoid hemorrhage associated with ischemic stroke [33]. Interestingly, CT also missed four hemorrhages, though all were identified as foci of hemorrhage within an acute ischemic infarct on MRI—the relevance of which remains uncertain in the context of hyperacute stroke treatment. A following prospective study from the same group confirmed that MRI is similar to CT in the diagnosis of intracranial hemorrhage in patients suspected to have acute ischemic stroke [34]; in this study the sensitivity of MRI and CT were 81% and 89%, respectively, and both were found to be 100% specific. Therefore, it appears that rare cases of early ICH may be missed on either MRI or CT, though hemorrhage missed on CT is typically either chronic or related to an ischemic infarct. Studies with tissue confirmation, allowing for measurement of the exact accuracy of both modalities, are lacking.

(iii) *Miscellaneous* Multiple attempts to obviate the need for imaging to exclude intracranial hemorrhage have failed, including clinical scores and lumbar puncture [35]. A few studies have explored transcranial ultrasound as an alternative to NHCT for identifying intracerebral hemorrhage, which may be a promising alternative in low-income countries without available access to a CT scanner, but this requires patients with an adequate acoustic window and an experienced sonographer [36, 37].

Does This Patient Have Hyperacute Ischemic Stroke?

Summary of Evidence NHCT is poor at identifying acute ischemic stroke [Strong Evidence]. CT perfusion imaging (CTP) and angiography (CTA) both modestly improve the accuracy of ischemic stroke diagnosis [Moderate Evidence]. MRI (diffusion-weighted imaging) is far superior to CT for identifying ischemic stroke within the first 12 h of symptom onset [Strong Evidence], but has not been shown to improve clinical outcomes and typically requires additional time relative to CT [Moderate Evidence], and thus cannot yet be recommended prior to IV-tPA in patients with suspected stroke presenting within 4.5 h of symptom onset. MRI helps to predict time of symptom onset [Moderate Evidence], and the safety of using MRI to treat patients with thrombolysis on this basis is established [Strong Evidence], but the efficacy remains unknown [Limited Evidence]. MRI may also be helpful in patients clinically unlikely to have a stroke but who would be thrombolytic candidates if proven otherwise [Limited Evidence].

Supporting Evidence

(i) *Computed tomography (CT)* NHCT images are commonly normal during the acute phase of ischemia. At times, patients may present with stroke-like symptoms due to non-stroke etiologies including postictal state following seizure, "complicated" migraine, brain tumor, toxic-metabolic conditions, acute peripheral vertigo, subdural hematoma, herpes encephalitis, demyelinating disease, or conversion disorder. Based purely on history and physical examination alone without confirmation by NHCT, stroke mimics may account for up to 13–19% of cases initially diagnosed with stroke [38, 39]. Diagnostic

accuracy improves when NHCT is used, but approximately 5% of cases are still misdiagnosed as stroke [40], which may improve to less than 2% at experienced academic centers treating patients with intravenous thrombolysis [19].

Increased scrutiny of hyperacute NHCT scans, especially following the early thrombolytic trials, suggests that some patients with large areas of ischemia may demonstrate subtle early signs of ischemia, even when imaged less than 3 h after symptom onset [41]. These early NHCT signs include parenchymal hypodensity, loss of the insular ribbon, obscuration of the lentiform nucleus, loss of gray and white matter differentiation, visualization of hyperdense clot in the region of the proximal middle cerebral artery (MCA) known as the "hyperdense MCA sign," subtle effacement of the cortical sulci, and local mass effect. Early changes are found in only 31% of NHCTs performed within 3 h of ischemic stroke, precluding its reliability as a positive sign of ischemia [42]. Early CT signs, however, are often subtle and difficult to detect even among experienced readers, though experience and expertise improve accuracy [43, 44].

Advanced CT imaging, including CT perfusion imaging (CTP) and CT angiography (CTA), may have increased sensitivity for ischemic stroke. CTP can detect areas of ischemic stroke by demonstrating either increased mean transit time or decreased cerebral blood flow in a vascular territory of the brain. A pooled analysis of 15 studies found a sensitivity of 80% and specificity of 95% for CTP as compared to DWI or follow-up MRI or CT as the reference standard [45]. False negatives were mostly due to lacunar infarcts or limited coverage. At one institution, the incremental benefit in diagnosing acute ischemic stroke with CTP over CTA and NHCT was found to be 12.4% and 18.2% over NHCT only [46]. Drawbacks of CTP include the requirement for contrast administration, increased radiation dosage, and limited coverage of the brain. CTA also improves the sensitivity for large ischemic stroke, either by identifying a large vessel occlusion or through a geographic paucity of vessels demonstrated on source images [47] but remains insensitive to small strokes.

(ii) *MRI diffusion-weighted imaging (DWI)* Unlike NHCT, DWI is capable of detecting very early physiologic changes during cerebral ischemia, demonstrating changes within minutes of ischemia in rodent stroke models [48–50]. Moreover, the sequence detects lesions as small as 4 mm in diameter [51]. The cause of signal alteration in DWI after acute ischemia is not entirely understood but is thought to reflect diffusion restriction predominantly in the intracellular space [52]. As duration of ischemia increases, a DWI lesion becomes progressively brighter with the added contribution of hyperintense T2 W signal known as "T2 shine through" [53]. To differentiate between true restricted diffusion and "T2 shine through," a bright DWI lesion should also show hypointense signal on the corresponding apparent diffusion coefficient (ADC) map, which is a more quantitative and direct measure of restricted diffusion.

The relatively high sensitivity and specificity of DWI for the detection of ischemia makes it an ideal sequence for positive identification of hyperacute stroke. Two studies evaluating DWI within 6 h of stroke onset reported 88–100% sensitivity and 95–100% specificity, using final clinical diagnosis as the reference standard [54, 55]. In another study, 50 patients were randomized to DWI or NHCT within 6 h of stroke onset and subsequently received the other imaging modality with a mean delay of 30 min [56]. Sensitivity and specificity of ischemia detection among blinded expert readers were significantly better with DWI (91% and 95%, respectively) compared to NHCT (61% and 65%). A recent large prospective study including 190 ischemic stroke patients assessed the accuracy of DWI compared to NHCT as a function of time from symptom onset [34]. As time from symptom onset increased, the sensitivity of DWI for

final diagnosis of ischemic stroke increased: 73%, 81%, and 92% for <3 h, 3–12 h, and >12 h, respectively, whereas NHCT had only 12%, 20%, and 16% sensitivity at these three respective time intervals [Strong Evidence].

Although DWI is the optimal test for imaging acute ischemia, the highest level data suggests that the sensitivity for detection within 6 h of onset is 81–91%; therefore, the absence of a DWI lesion does not rule out ischemia. False negatives have been reported in small subcortical and brainstem infarctions and in patients with low National Institutes of Health Stroke Scale (NIHSS) scores [34, 55, 57–59]. Furthermore, within the first 6 h of stroke onset, DWI demonstrates delayed signal evolution after changes in perfusion [60]. Restricted diffusion has been reported with other nervous system pathologies such as brain abscesses [61], herpes encephalitis [62], Creutzfeldt-Jakob disease [63], highly cellular tumors such as lymphoma or meningioma [64], seizures [65], and hypoglycemia [66]. However, the clinical history and appearance of these lesions on the remaining standard MR sequences should allow for diagnosis of these different pathologies. Diagnosis of ischemic stroke with DWI should be interpreted in conjunction with conventional MR sequences and within the proper clinical context.

Regarding CT versus MRI for first-line imaging in patients with suspected acute ischemic stroke, several critical factors have not been adequately studied. These factors include practicality (including scanner, technician, and radiologist/neurologist access round the clock, patient eligibility and tolerability, and scan duration), cost-effectiveness, and effect on clinical decision-making and patient outcomes. A large study assessing CT vs. MRI for diagnosis of acute ischemic stroke excluded 11% of patients due to issues such as patient intolerability and claustrophobia in the MR scanner, MR contraindications such as pacemaker placement, and medical instability [34]. One study compared the cost-effectiveness of immediate vs. delayed NHCT for all patients compared with a subset of acute stroke patients and found that an immediate NHCT in all patients was more cost-effective than delayed NHCT in a subset of patients [67]. However, similar studies have not yet been performed for MRI and are greatly needed.

Recent advances have shown that MRI fluid-attenuated inversion recovery (FLAIR) sequences can determine whether an ischemic stroke identified by DWI is <4.5 h in age or not. Ischemic strokes that demonstrate diffusion restriction but no correlate on FLAIR imaging were typically <4.5 h in age, while those with a correlate on FLAIR imaging were typically >6 h in age [68–70], though an exact cut-off value for subtle FLAIR hyperintensity relative to the contralateral normal parenchyma remains to be determined. A large safety trial in the United States [71] demonstrated that using MRI to identify hyperacute stroke patients for intravenous thrombolysis results in a hemorrhage rate less than that identified in ECASS III [72]. At the time of this writing, another trial in Europe [73] is underway to evaluate the efficacy of this approach in improving neurological outcomes.

In some circumstances, patients may present with symptoms clinically unlikely to be due to stroke, but the possibility of stroke cannot be completely excluded. MRI can occasionally be performed quickly enough to leave time for IV-tPA in case an acute ischemic stroke is identified [21, 74]. No trial has yet determined whether administering IV-tPA in this setting improves outcomes or not.

Is This Ischemic Stroke Likely to Hemorrhage After Intravenous Thrombolysis?

Summary of Evidence The risk of hemorrhage and poor outcomes after intravenous thrombolysis increases in the presence of early CT signs of infarction and low ASPECTS score [Strong Evidence]. Nevertheless, within the 3 h window, IV-tPA continues to benefit these patients at higher risk [Moderate Evidence]. Patients with a large MCA stroke may not benefit from IV-tPA in the 3–4.5 h window due to increased risk of

hemorrhagic conversion [Limited Evidence]. Novel imaging techniques with CT and MRI improve our ability to predict hemorrhagic conversion, but none is proven to identify patients that will not benefit from IV-tPA [Limited Evidence].

Supporting Evidence

(i) *Computed tomography (CT)* Early CT signs of infarction, especially involving more than one-third of the MCA distribution, have been reported to be associated with severe stroke, increased risk of hemorrhagic transformation [75–77], and poor outcome [78]. Recently, ECASS-3, which demonstrated efficacy of intravenous tPA administration within 3–4.5 h after stroke onset, excluded patients with early signs of stroke in greater than 1/3 of the MCA territory [14]. In contrast to ECASS-3, the National Institute of Neurological Disorders and Stroke tPA trial [13] did not exclude patients with early CT signs, and subgroup analysis has shown that IV-tPA continues to benefit patients with early CT signs of ischemic stroke [7]. Therefore, early CT signs should not be used to exclude patients who are otherwise eligible for thrombolytic treatment within 3 h of stroke onset.

The Alberta Stroke Program Early CT Scores (ASPECTS), a 10-point semiquantitative scoring system, was developed as a tool for detection of early ischemic changes on noncontrast head CT that would be more reliable and prognostic than simple visual inspection of the MCA territory [41, 79]. A normal ASPECT score is 10 with 1 point subtracted for each abnormal brain region (of 10, 7 cortical and 3 subcortical) within the affected hemisphere. Both methods (visual inspection and ASPECTS) require training to ascertain subtle ischemic changes, and ASPECTS remains vulnerable to inter-rater variability [80].

(ii) *Magnetic resonance imaging (MRI)* Compared to NHCT, DWI is highly sensitive to acute ischemic stroke and can delineate the ischemic core that is likely to represent the final infarct as defined by follow-up MRI [34]. Large infarcts are more likely to develop hemorrhagic transformation and result in poor outcomes [77, 81, 82]. The volume of a stroke with very low apparent diffusion coefficient (ADC) values also predicts hemorrhagic transformation [81]. Novel techniques, such as measurement of parenchymal enhancement [83], permeability imaging [84], or perfusion imaging [85], may be better able to predict which strokes are likely to develop hemorrhagic transformation after thrombolysis. The number of microbleeds detected on susceptibility-weighted sequences (T2* and SWI) also predicts the risk of hemorrhagic transformation [86–90]. However, no study demonstrates that patients identified to be at heightened risk based on MRI will not benefit from IV-tPA, neither within the 3 h nor the 3–4.5 h windows. Thus, the role of MRI in determining whether to continue with IV-tPA or not in an otherwise eligible patient remains in question.

Applicability to Children

No prospective clinical trial to date has investigated the use of intravenous thrombolysis in children under the age of 16. An attempt to perform a randomized evaluation of thrombolysis in pediatric stroke was halted due to poor accrual [91]. Thus, none of the recommendations above may apply to children. Pediatric stroke is further complicated by protean etiologies, many different than those typically seen in adults, an immature fibrinolytic system, and a far lower prevalence that resists establishment of efficient rapid systems of care.

Should This Patient Undergo Endovascular Thrombectomy?

In October 2014, the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial had completed and announced significantly improved outcomes in patients treated

with endovascular thrombectomy (EVT) and IV-tPA as compared to IV-tPA alone [8]. Subsequently, other similar RCTs were halted, including the trials: Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE), Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT-PRIME), Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND-IA), and Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT). These all showed significant or nearly significant improvements in outcomes with EVT, establishing EVT as the new standard of care for hyperacute stroke patients with large vessel occlusion (LVO) [92–95] [Strong Evidence]. EVT was shown to be highly efficacious and consistent, demonstrating an absolute risk reduction of poor outcome ranging from 14% to 33% across the five different trials. The time window for these trials (stroke onset to anticipated time to endovascular treatment) varied from 6 h to 12 h, though the vast majority of patients were enrolled within the 6 h time window. Nearly all patients first received IV-tPA prior to EVT, unless specifically contraindicated. In contrast to prior neutral RCTs evaluating EVT (IMS-3, SYNTHESIS Expansion, and MR RESCUE) [96–98], a stent retriever device was used in the vast majority of cases, sometimes supplemented with clot aspiration.

Another critical departure between the prior neutral RCTs and the recent positive RCTs for EVT was that the positive RCTs required patients to have LVO demonstrated by noninvasive imaging, nearly always with CTA. Given that the presence of LVO is a prerequisite for endovascular thrombectomy and that the majority of hyperacute stroke patients will not have an LVO [99], determining the presence of LVO in a hyperacute stroke patient is a critical step in evaluating patients for EVT candidacy [Strong Evidence] (Question 2.1).

The recent RCTs varied greatly according to inclusion and exclusion criteria. A key exclusion criterion in three of the trials (ESCAPE, SWIFT-PRIME, and EXTEND-IA) was the presence of a large ischemic "core" [92, 93, 95] (Question 2.2). Though conceptually a large ischemic core is meant to reflect a large completed infarct that could not be salvaged, the definition of how to measure the ischemic core varied across the three trials. MR CLEAN also evaluated the presence of a large ischemic core using ASPECTS scoring of NHCT but did not require exclusion of any patients on this basis [8]. Subgroup analysis of the MR CLEAN data shows that when ASPECTS score was very low (0–4), EVT (with IV-tPA) provided no statistically significant benefit as compared to IV-tPA alone (odds ratio for good outcome 1.09), though the number of patients in this subgroup was low. A pooled analysis of the five positive RCTs similarly found insufficient evidence to support EVT in treating patients with a low ASPECTS [9]. Further, trials that excluded patients with a large ischemic core (ESCAPE, SWIFT-PRIME, and EXTEND-IA) had overall improved outcomes compared to those that did not. While the exact role of measuring an ischemic core prior to EVT remains to be determined, it is likely of consequence as an important tool to limit "futile" EVT [Moderate Evidence].

Another commonly held hypothesis is that EVT may only improve outcomes in patients who have "salvageable" parenchyma that is vulnerable to infarct, frequently conceptualized as a "penumbra" around an ischemic core (Question 2.3). Both CT and MRI perfusion imaging attempts to directly measure a penumbra by establishing thresholds for particular perfusion parameters for an ischemic core and subtracting this from surrounding oligemia to determine a "penumbra" or "mismatch volume"; in some cases, the ischemic core may also be compared to the clinical status of the patient, i.e., "clinical imaging mismatch." Identifying the adequacy of collateral flow to an affected territory has also been used to identify potentially salvageable parenchyma. The underlying assumption here is that adequate collaterals will help protect vulnerable tissue from infarct long enough for EVT to

remain effective. One RCT explicitly tested the efficacy of penumbra evaluation with perfusion-diffusion mismatch MRI in patients subsequently undergoing EVT [98]. While this trial found no benefit for EVT in either group undergoing or not undergoing penumbra evaluation [Strong Evidence], this trial did not use stent retrievers and thus is not adequately informative for current practice. Another trial evaluated the use of a new thrombolytic agent (tenecteplase) versus IV-tPA after only including patients with a penumbra as assessed with CTP; this trial found improved outcomes with the new thrombolytic agent, but since it did not randomize patients to no CTP, it does not directly test the use of penumbra imaging to select patients for tenecteplase [100] [Limited Evidence].

The more recent positive RCTs for EVT varied widely in both their use and definition of salvageable tissue for patient inclusion and exclusion. A meta-analysis of these results demonstrated that in patients selected by having adequate or good collaterals on multiphase CTA or small ischemic core/adequate penumbra on perfusion imaging, EVT likely improved outcomes in patients beyond 6 h and up to 7.3 h [12] [Moderate Evidence]. Finally, at the time of this writing, a trial using a "clinical imaging mismatch" paradigm to select patients beyond the 6 h window was stopped early following a prespecified interim analysis due to strong efficacy [101]; along with DEFUSE-3, another stopped trial that used imaging mismatch to select patients for EVT beyond 6 h, these trials now strongly support the use of perfusion imaging to select patients beyond 6 h for EVT [evidence level pending publication of results].

Does This Patient Have a Large Vessel Occlusion?

Summary of Evidence CTA is an accurate and highly efficient method to evaluate for LVO in hyperacute stroke patients [Strong Evidence], which is critical in determining which patients may benefit from EVT [Strong Evidence]. The risk of permanent contrast nephropathy in stroke patients is sufficiently low that the delay imposed by evaluating renal function prior to CTA is not routinely warranted [Moderate Evidence]. MRA without contrast (i.e., time-of-flight MRA) is equivalent to CTA in evaluating for intracranial LVO [Moderate Evidence], and MRA with contrast is equivalent or superior to CTA in evaluating the extracranial vasculature [Strong Evidence], but MRA often imposes additional delays to treatment, which can worsen outcomes [Strong Evidence]; thus MRA should be reserved for patients who absolutely cannot undergo CTA or who are already undergoing MRI. Other techniques such as transcranial Doppler imaging or clinical assessment is not yet sufficiently accurate to replace CTA [Limited Evidence].

Supportive Evidence

(i) *Digital subtraction catheter-directed angiography (DSA)* The gold standard for assessing large vessel occlusion is currently DSA. Given the high spatial and temporal resolution of DSA as compared to other techniques, occlusion and stenosis of both large and small vessels are readily demonstrated (however, for note of controversy, see [102]). The dynamic images from DSA also help in evaluating collateral flow. The major drawbacks of DSA are that it requires (1) groin puncture to access the femoral artery subjecting the patient to potential groin complications including hemorrhage and pseudoaneurysm; (2) the use of intra-arterial wires and catheters to select target vessels for angiography, which may result in stroke or arterial injury; and (3) availability of experienced operators, technologists, and nurses to perform the procedure. On the other hand, DSA is a prerequisite to EVT and, if positive, can lead directly to EVT.

Most patients in the IMS-3 trial were evaluated with a "DSA-first" approach, whereby patients suspected to have LVO based on clinical assessment were taken directly to the angiography suite for DSA and then EVT if LVO was detected [96]. The IMS-3 trial showed no benefit for EVT with this approach, though older-generation thrombectomy devices (and not stent retrievers) were used in the vast majority of these patients. In contrast, the recent RCTs that

were positive for EVT all required noninvasive evidence of LVO prior to EVT [8, 92–95]. It is difficult to determine how much noninvasive LVO detection contributed to the success of the recent RCTs, as compared to use of stent retrievers and improved systems of care. However, while the evidence does not fully prove that non-DSA-based LVO detection itself leads to improved outcomes, the preponderance of evidence strongly supports noninvasive LVO detection in hyperacute stroke patients as a prerequisite to EVT. As discussed further below, noninvasive LVO detection also improves systems of care that involves more hospitals without local access to neurointerventional services.

(ii) *Computed tomographic angiography (CTA)* While a hyperdense vessel on NHCT is suggestive of thrombus in the M1 segment or basilar artery, this sign is variably present and not sensitive nor entirely specific to the presence of LVO [103]. Ongoing efforts to improve LVO detection with thin-section NHCT may improve the accuracy of this sign in the future [104, 105]. Given improvements in CT scanners over the past decade, largely due to multidetector row technology, it is now possible to evaluate the cerebral vasculature highly accurately with CT and high-rate intravenous contrast administration. With proper technique, CTA delineates the course and caliber of the carotid and vertebral arteries in the neck, the internal carotid and basilar arteries intracranially, and the proximal portions of the anterior, middle, and posterior cerebral arteries [106]. When an occlusion of one of these vessels is present, contrast opacification of the vessel is absent, providing evidence for the occlusion.

One advantage of CTA is that it can be performed immediately following the prerequisite noncontrast CT for all stroke patients. The entire examination can be completed within a few minutes using 75–100 mL of nonionic intravenous contrast. CTA has been found to be both sensitive and specific in identifying a large vessel occlusion (defined as A2, M2, P2, or more proximal) in comparison to catheter angiography [102, 106], including several small case series [107–113]. CTA is also accurate in measuring large vessel stenosis. One study with two blinded raters comparing CTA to DSA measured 475 short segments of intracranial arteries in 41 patients [114]. For detection of ≥50% stenosis, CTA had 97.1% sensitivity and 99.5% specificity. A meta-analysis of eight high-quality studies and 864 patients compared carotid stenosis as measured by CTA to DSA [115]. For 70–99% internal carotid artery (ICA) stenosis, the overall sensitivity and specificity were 85% and 93%, respectively. For detection of ICA occlusion, the sensitivity and specificity were 97% and 99%, respectively. Analysis of the recent RCTs for EVT regarding CTA accuracy is pending but is widely expected to demonstrate similar or better accuracy. The accuracy of CTA interpretation increases with the training and experience of the physician [116]. In our experience, 3D reconstructions using maximum intensity projections (MIPs) and volume rendering both improve the accuracy of CTA interpretation, though the use of these techniques in the hyperacute period should be balanced against the additional delay incurred by performing these reconstructions.

There are several pitfalls in the use of CTA for identifying LVO [106, 117, 118]. Flow in an affected vessel may be slowed sufficiently for contrast opacification to be absent proximal to the occlusion, leading to inaccurate determination of the length of occlusion and possible incorrect interpretation of an occlusion arising from a proximal trunk such as the common carotid artery; this can be overcome in many instances with delayed or multiphase CTA [119, 120], but the diagnostic yield and effect on outcomes of performing delayed or multiphase CTA remain uncertain [121]. Also, incorrect contrast bolus timing can lead to poor opacifica-

tion of the cerebral arteries when too early or excessive venous contamination when too late. Identifying occlusion of smaller branches, such as M3 vessels or the anterior inferior cerebellar artery (AICA), is also difficult due to the limited resolution of CTA imposed by radiation dose limits.

One concern regarding CTA is the risk of contrast-induced nephropathy (CIN). Several studies have addressed this by measuring the rate of CIN in acute ischemic stroke patients following CTA. Despite varying definitions of CIN, these consistently demonstrate a very low rate of CIN (2–5%) in patients undergoing CTA for stroke and virtually no patient requiring hemodialysis as a result of CIN [122–126]. A recent study further compared patients undergoing contrast-enhanced CT for any reason to those undergoing noncontrast-enhanced CT [127, 128]. This study found that the rate of acute renal failure was not significantly different between the two groups. No study has prospectively randomized patients to contrast administration versus no contrast, so definitive evidence regarding the risk of CIN specifically (as compared to any cause acute renal failure) is lacking. The time required to evaluate for pre-existing risk factors for CIN, including serum creatinine, diabetes, and heart failure, will vary across hospitals but is likely to require at least a few additional minutes of time prior to performing the CTA. Thus, there is no evidence to support checking a serum creatinine prior to CTA in the hyperacute setting and in fact at least moderate evidence to the contrary.

(iii) *MR angiography (MRA)* MRA is capable of imaging the intracranial vasculature without contrast using a time-of-flight technique and also via contrast-enhanced MRA. For proximal ICA lesions, the sensitivity and specificity of contrast-enhanced MRA are high when compared to DSA. In a meta-analysis of 41 studies in 2541 patients looking at ICA lesions of 70–99% stenosis on DSA, contrast-enhanced MRA was found to be the most sensitive (94%) and specific (95%) of four modalities: enhanced MRA, non-enhanced MRA, Doppler ultrasound, and CTA [115]. While MRA appears to be a useful tool for measuring stenosis in large vessels, its sensitivity decreases for smaller caliber intracranial vessels. Although contrast-enhanced MRA of the extracranial arteries appears to be better at defining the degree of stenosis than time-of-flight MRA [129, 130], assessment of the intracranial vessels with contrast is limited due to venous contamination and poor spatial resolution. In the study of intracranial disease discussed above comparing CTA and MRA to DSA, in 28 patients (in 672 vessel segments) time-of-flight MRA had a sensitivity of 70% and 81% and specificity of 99% and 98% for intracranial stenosis and intracranial occlusion, respectively [102]. The Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) trial was a prospective, multicenter study comparing the diagnostic accuracy of transcranial Doppler (TCD) and MRA to DSA [131]. The SONIA study found that both TCD and MRA have high negative predictive values (86% and 91%, respectively) but low positive predictive values (36% and 59%, respectively). Sensitivity and specificity could not be obtained since not every patient had DSA. As noted previously, the major limitation to MRA is the increased time required to perform MRI compared to CT in most institutions. However, MRA may be useful in select circumstances where patients are already undergoing brain MRI in the hyperacute stroke period.

(iv) *Miscellaneous* As noted above, TCD was evaluated in the SONIA study and was found to have a modestly high negative predictive value, but a low positive predictive value for detecting intracranial atherosclerosis [131]. As for MRA, the diagnostic performance of TCD may improve in the more limited clinical context of attempting to detect LVO. However, TCD requires an adequate temporal acoustic window to evaluate

for MCA occlusion, which may not be present in approximately 20% of patients. Thus, TCD cannot be recommended currently as a replacement for CTA. Clinical assessment with the National Institutes of Health Stroke Scale (NIHSS) has been investigated as a tool to predict which patients may or may not have LVO. Interestingly, LVO is found variably in patients with NIHSS ranging from 2 to 20 [99]. Thus the NIHSS cannot be recommended as a surrogate for LVO detection. Usage of a NIHSS cutoff to determine which patients to screen for EVT is beyond the scope of this chapter but should be determined based upon the clinical inclusion and exclusion criteria for EVT rather than its predictive value for LVO.

Does This Patient Have a Large Ischemic Core?

Summary of Evidence The size of an ischemic core as defined by DWI accurately predicts a final infarct size and outcomes in acute stroke patients [Strong Evidence]. A low ASPECTS score on NHCT also predicts larger final infarct size and worse outcomes, though not as robustly as DWI [Strong Evidence]. A large ischemic core identifies patients unlikely to benefit from EVT, when defined by either a very low ASPECTS score (0–4) [Moderate Evidence] or by a large DWI lesion [Limited Evidence]; however, performing MRI may also introduce delay to therapy. Other methods to define the ischemic core, including CTA source images (CTA-SI) and CT or MR perfusion imaging, may also be accurate in predicting final infarct size and outcomes, in particular using relative cerebral blood flow maps with CT perfusion imaging [Strong Evidence].

Supporting Evidence

(i) *Computed tomography (CT)* While NHCT remains poorly sensitive to hyperacute ischemic stroke, early signs of ischemia when present predict larger final infarct size and worse outcomes [75–78]. Among other trials, the positive ECASS-3 trial, which showed efficacy of IV-tPA in improving outcomes within the 3–4.5 time window, excluded patients with NHCT signs of ischemic stroke that involved greater than 1/3 of the MCA territory [14]. However, while this criterion predicts worse outcomes overall, it does not necessarily negate the benefit of IV-tPA [7].

ASPECTS was devised as an ordinal scoring method to more reliably determine the extent of early signs of ischemic stroke on NHCT [41, 47, 79]. As noted above, the score ranges from 0 to 10, with a point lost for each of ten MCA territory regions demonstrating features of ischemic stroke including loss of gray-white matter distinction and hypodensity. In the ESCAPE trial, an ASPECTS <6 was used as a criterion to exclude patients from enrollment [93]. Subsequent analysis found that of the patients enrolled, 3.6% had an ASPECTS <6 based on core lab review, suggesting that using a cutoff of <6 may be reliable, though it is unknown what percentage of patients excluded from the trial due to a low ASPECTS would have been included if their ASPECTS was determined by a core lab. SWIFT-PRIME and REVASCAT also excluded patients with a low ASPECTS score (<7). MR CLEAN included patients with any ASPECTS score, at the discretion of the treating physicians, including 28 patients with an ASPECTS of 0–4 [8]. Subgroup analysis found benefit of EVT in patients with ASPECTS 8–10 (odds ratio for good outcome favoring EVT [OR] 1.61) and 5–7 (OR 1.97), but no benefit when ASPECTS was 0–4 (OR 1.09). However, the number of patients in the last group was small resulting in large confidence intervals (OR 95% CI 0.14–8.46). A subsequent pooled analysis of five of the positive RCTs comparing stent retriever-based EVT versus best medical therapy also found no significant benefit for EVT in patients with ASPECTS of 0–5, though again with small sample size (n = 121, OR 1.24, 95% CI 0.62–2.49) [9].

The size of an infarct can also be predicted using the CTA-SI, by measuring the region of hypodensity and hypovascularity in

the affected territory, as compared to DWI [132, 133], but may overestimate infarct core depending on the protocol used [134, 135]. CTP may also be used to predict infarction by setting a low perfusion threshold below which tissue is presumed to represent the ischemic core. Studies vary greatly in terms of the perfusion parameter and threshold used to determine an ischemic core. For example, a large series of 130 patients found good accuracy (AUC = 0.927) for an absolute CBV threshold of 2.0 mL × 100 g^{-1} [136]. More recent efforts have demonstrated that a relative cerebral blood flow (CBF) of less than 30–34% or CBV of less than 32–34% is [137] highly accurate of ultimate infarct volume; this latter threshold has further validity in that it was used to select patients in the recently halted DAWN and DEFUSE-3 trials (see Question 2.3).

(ii) *Magnetic resonance imaging (MRI)* When tissue infarcts, it results in increased diffusion restriction both intracellularly and extracellularly, resulting in marked decreased apparent diffusion coefficients (ADC) and hyperintensity on the trace DWI images. Several studies have confirmed that the resulting region of diffusion restriction represents infarcted tissue demonstrated on subsequent follow-up MRI [34, 53, 54, 138–141]. Patients with an initial DWI lesion >70 mL demonstrate a very high rate of poor outcomes [142]. Prior to the recent RCTs but after the introduction of stent retrievers, DWI was used in one study to exclude patients from EVT with a large infarct >70 mL [143]. They investigated outcomes before and after introducing this exclusion criterion and found that outcomes improved significantly after they began using DWI for this purpose. EXTEND-IA and initially SWIFT-PRIME both used DWI definitions of ischemic core to exclude patients with large completed infarcts but do not provide independent evidence that using DWI in this fashion appropriately excludes patients from futile EVT [92, 95]. It is thus probable, but not certain, that DWI can identify patients in whom EVT will be futile. As with any MR-based method, a drawback of DWI is that it may delay treatment [144].

Does This Patient Have "Salvageable" Tissue?

Summary of Evidence Methods to define salvageable tissue vary widely and include perfusion-based techniques as well as assessment of collateral flow to the affected territory, with no clearly defined gold standard. The presence of salvageable tissue based on perfusion imaging does not identify patients more likely to benefit from older-generation EVT methods [Strong Evidence]. Selection of patients based on the presence of a penumbra with perfusion imaging or adequate collaterals with multiphase CTA may help to identify increased benefit from stent retriever-based EVT but may not be necessary and could possibly exclude patients who would otherwise benefit from EVT within 6 h of stroke onset [Moderate Evidence]. A trial that explicitly randomizes patients with *unfavorable* penumbra/collateral imaging (i.e., no or little mismatch or poor collaterals) for EVT or not would be required to determine whether or not it is necessary to apply such imaging in the first 6 h. On the other hand, growing evidence indicates that patients with *favorable* penumbra/collateral imaging might benefit from EVT beyond 6 h [Strong Evidence, pending publication of results].

Supporting Evidence

(i) *Penumbra-based methods* When arterial flow is severely disrupted, a portion of the brain parenchyma in the affected arterial territory may experience ischemia. The depth and length of this ischemia determine whether the tissue will experience irreversible infarction. The idea of a penumbra defines a region surrounding or adjacent to infarcted tissue that is ischemic and thus vulnerable to future infarction but also potentially salvageable if the ischemia is reduced or abated within a certain time period. Thus,

the goal of therapy is to save this penumbra from subsequent infarction through recanalization or other methods.

Early studies used PET-based oxygen and blood flow tracer imaging to identify thresholds of oxygen metabolism and blood flow that identified tissue destined to infarct versus tissue that was ischemic but that did not necessarily infarct (i.e., penumbra) [145]. Since then, both CT- and MR-based perfusion imaging have been used in a similar fashion [136, 146–148]. Taking advantage of the blood oxygenation level-dependent (BOLD) relaxation effect, MR-based CMRO2 measurements have also been recently used for similar purpose [149, 150]. A common feature of all of these methods is to define one threshold to represent ischemic tissue and to either define another threshold to define the ischemic core or to use another measure (e.g. DWI) to define the ischemic core. The mismatched area between ischemic tissue and the infarcted core is then used to define the penumbra.

In a prospective study, MR perfusion-diffusion mismatch identified patients more likely to experience a good outcome following reperfusion, suggesting that this method is effective at least as a prognostic indicator [151]. Another study randomized patients to MR perfusion-diffusion mismatch-based penumbra imaging versus no MR imaging to determine whether the former selected patients would uniquely benefit from EVT [98]. This study found no evidence that penumbra detection with MR perfusion-diffusion mismatch would select patients appropriately for EVT. However, this study was performed before stent retrievers were widely used and is thus limited to EVT performed with older-generation devices. Subsequently, no similar study has been performed. A few of the recent RCTs proving the efficacy of EVT employed perfusion-based penumbra imaging as an inclusion criteria, two with perfusion imaging (EXTEND-IA and SWIFT-PRIME) [92, 93, 95]. While these trials showed increased efficacy of EVT compared to trials that did not require penumbra imaging (MR CLEAN and REVASCAT), the multiple differences between the trials preclude distinction of which factors resulted in different effect sizes among the trials. Also, efficacy of EVT was sustained in trials that did not require penumbra imaging, suggesting that penumbra imaging might inappropriately exclude patients who could benefit from EVT. Interestingly, SWIFT-PRIME changed their inclusion/exclusion criteria after enrolling several dozen patients, creating an opportunity to see how penumbra imaging might affect outcomes [95]; however the sample size for this analysis may be underpowered due to the trial being halted early after the announcement of the MR CLEAN results.

Another trial used advanced CT imaging, CTA and CTP, to select patients for a prospective randomized controlled trial of intravenous tenecteplase versus alteplase for intravenous thrombolysis within 6 h of symptom onset [100]. This trial found benefit for tenecteplase. A subsequent similar prospective randomized controlled trial of intravenous tenecteplase versus alteplase found no benefit, suggesting that the advanced imaging was important in realizing the added benefit of tenecteplase [152]. Unfortunately, it cannot be determined based on these trials whether the difference in trial outcomes was due to selecting patients on the basis of CTA for LVO, CTP for a small ischemic core, CTP for an adequate penumbra, or a combination of these factors.

More recent trials, including the "DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention" (DAWN) trial and the "Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3" (DEFUSE-3) trial, aim to determine the efficacy of EVT in stroke patients presenting beyond 6 h of stroke onset. The DAWN trial applies a "clinical imaging mis-

match" paradigm that includes measurement of an ischemic core with MRI-DWI or CTP (relative cerebral blood flow <30%) and compares this to NIHSS score and age; patients presenting 6–24 h after onset with high NIHSS relative to the size of their ischemic core are then randomized to EVT or not. Though not yet published at the time of this writing, the trial was stopped early following a prespecified interim analysis due to efficacy [101]; if confirmed positive, this will strongly support the use of perfusion imaging to select patients beyond 6 h for EVT [evidence level pending publication of results]. The also halted RCT DEFUSE-3 similarly aimed to determine the efficacy of EVT in patients presenting between 6 and 16 h of stroke onset, selected using CTP- or MRI-based penumbra imaging.

(ii) *Collateral flow-based methods* In order for tissue to remain viable despite parent artery occlusion, there must be blood flow from a collateral source—most frequently from arteries in adjacent territories [145, 153]. A brain with large collaterals is therefore more likely to have salvageable tissue than one without. This forms the basis of collateral flow imaging. Several methods have been employed to assess collateral flow in stroke patients, including DSA, PET, MRA, and FLAIR imaging which may show hyperintense pial collaterals in the affected territory and CTA [145, 154–156]. The presence of good collateral vessels has been a strong predictor of good outcomes, independent of treatment.

In one of the recent positive RCTs for EVT (ESCAPE), a multiphase CTA technique was used to determine the presence of collateral vessels over the affected territory [93]. The presence of collaterals was graded as good or poor based on a visual grading system. Patients were included in the trial if collaterals were deemed to be good. A meta-analysis of 5 of the positive RCTs for EVT found that patients with good collaterals on multiphase CTA or adequate penumbra on perfusion imaging might benefit from EVT up to 7.3 h after onset [12]. Thus, these techniques are appropriate to select for patients between 6 and 7.3 h. However, as patients were not randomized to multiphase CTA/penumbra imaging versus no such selection criteria, using this advanced imaging to select patients for EVT within 6 h of onset remains in question.

Applicability to Children

As for intravenous thrombolysis, no prospective and/or controlled study to date has evaluated the safety nor efficacy of endovascular therapy for ischemic stroke in children. Thus, none of the recommendations above necessarily nor sufficiently apply for pediatric stroke.

How Can We Improve Systems of Stroke Care and Imaging to Expedite Treatment of Hyperacute Stroke Patients?

Summary of Evidence Time to intravenous thrombolysis and EVT greatly influences outcomes [Strong Evidence]. Improving systems of stroke care, including imaging in the hyperacute setting, is thus likely to improve neurological outcomes. Value stream analysis (VSA) and mapping techniques may improve door-to-needle [Moderate Evidence] and door-to-groin puncture [Limited Evidence] times. Performing initial evaluation and intravenous thrombolysis in the CT scanner room significantly improves door-to-needle times [Moderate Evidence]. Ambulatory stroke units that include mobile CT scanners may also improve door-to-needle times and are safe [Moderate Evidence]. New multidisciplinary approaches to stroke care are likely needed to improve outcomes from intravenous thrombolysis and EVT [Limited Evidence].

Supporting Evidence Time to intravenous thrombolysis from symptom onset is a significant predictor of both 3-month outcomes and the relative benefit derived from IV-tPA [20].

Similarly, time to reperfusion by EVT was recently shown to be a significant predictor of outcomes and the relative benefit from EVT, perhaps with an even larger effect than that shown for IV-tPA [8, 11]. Hence, minimizing the time to treatment is of paramount importance to optimize stroke outcomes.

There are many elements to the evaluation and treatment of stroke patients, involving a variety of health-care professionals (including but not limited to physicians, nurses, technicians, radiology technologists, emergency medical transport personnel, and pharmacists), a variety of settings (the patient's home, ambulance or other vehicle, the CT or MR scanner, the emergency room, and the angiography suite), and a variety of assessments and decisions. Establishing door-to-needle and door-to-groin puncture guidelines, particularly those tied to accreditation, may help reduce the time to treatment in these settings [157]. Protocols for rapid thrombolysis in the Emergency Department have been developed and appear to be transferrable to other institutions [158–160]. Value stream analysis (VSA) is a technique originally developed to improve the efficiency of industrial manufacturing processes and has since been applied to the evaluation and treatment of hyperacute stroke patients leading to significant decreases in door-to-needle times. Based on these findings, guidelines from the American Stroke Association encourage direct admission of patients to the CT scanner with intravenous thrombolysis provided in the scanner suite if the patient is eligible [161].

Another method to decrease door-to-needle time is to employ a mobile stroke unit that includes a CT scanner [162–164]. The patient and a NHCT can be assessed in this unit via telemedicine methods. This method has been successfully deployed in Europe and the United States. A randomized trial suggests that this technique is safe and reduces time to intravenous thrombolysis [165]. More evidence is required to see how this approach affects time to EVT.

Table 8.1 Diagnostic performance for patients presenting with acute neurological deficits

	Sensitivity (%)	Specificity (%)	Evidence
Acute intraparenchymal hemorrhage (<6 h)			
CT	89–100[a]	100[a]	a
MRI	81–100	100	Strong
Acute subarachnoid hemorrhage (<12 h)			
CT	98–100	100	Strong
MRI (FLAIR)	92–100	100	Limited
Acute ischemic infarction (<6 h)			
CT	31–61	65	Moderate
MRI	88–100	95	Strong
Large vessel occlusion (intracranial)			
CTA	97	99	Strong
MRA	81	98	Moderate

Adapted from Vo KD, Lin W, Lee J-W. Neuroimaging in Acute Ischemic Stroke. In Medina LS, Blackmore CC (eds): *Evidence-Based Imaging: Optimizing Imaging in Patient Care.* New York: Springer Science + Business Media, 2006, with kind permission of Springer Science + Business Media

[a]Although the exact sensitivity or specificity of CT for detecting intraparenchymal hemorrhage is unknown (limited evidence), it serves as the gold standard for detection in comparison to other modalities

Take-Home Table and Figure

Table 8.1 highlights the diagnostic performance of imaging for acute neurological deficits. Figure 8.1 is an imaging algorithm for patients with suspected hyperacute ischemic stroke.

Take-Home Points

Imaging of patients with hyperacute ischemic stroke should be driven by its ability to enable and direct subsequent therapies that are *proven* to improve outcomes—namely, intravenous thrombolysis and endovascular thrombectomy. The choice of imaging must also weigh its utility against time delays to treatment in order to optimize patient outcome. For most Emergency Departments, CT represents the best balance of

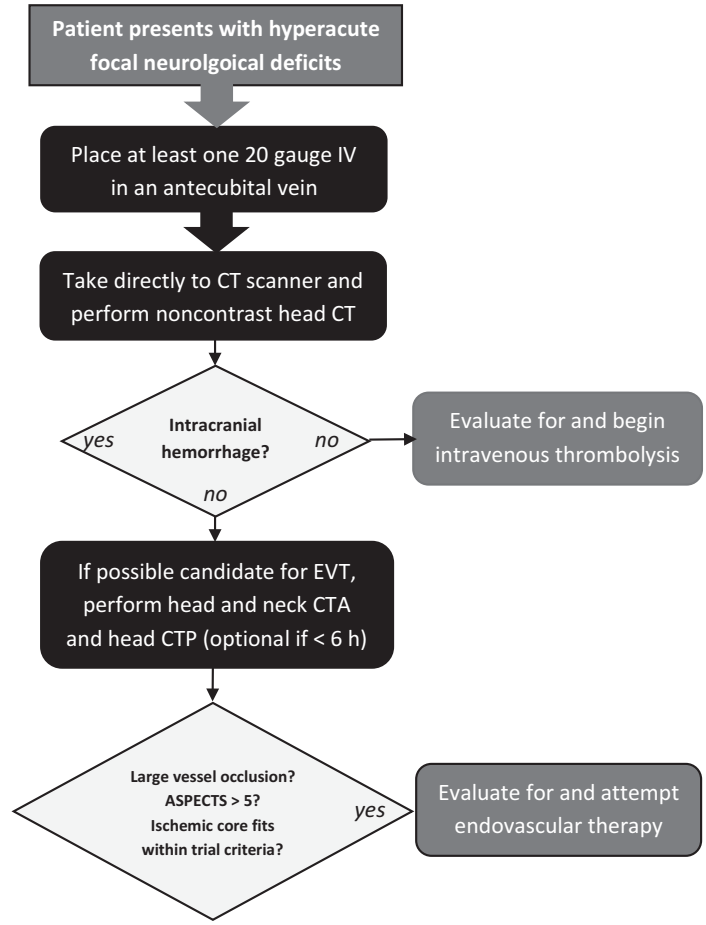

Fig. 8.1 Suggested simplified imaging pathway for patients with suspected hyperacute ischemic stroke

accuracy and availability, allowing detection of intracranial hemorrhage, large vessel occlusion, and very large ischemic cores to permit rapid decisions on whether to proceed with intravenous thrombolysis and/or endovascular thrombectomy. MRI is essentially equivalent in these tasks but typically introduces unnecessary delays to treatment. Advanced techniques, including perfusion and collateral imaging, will likely soon have an evidence-based role particularly beyond 6 h since stroke onset and will also need to be incorporated into the armamentarium of the radiologist.

Imaging Case Studies

Case 1

In Fig. 8.2a–c, a patient presents with sudden-onset left-sided weakness, confusion, and neglect within 2 h of onset. Large vessel occlusion with hyperacute stroke is established.

Case 2

In Fig. 8.3a–c, acute or hyperacute infarct in the left corona radiata is discovered after a patient presents with sudden-onset right hemiparesis.

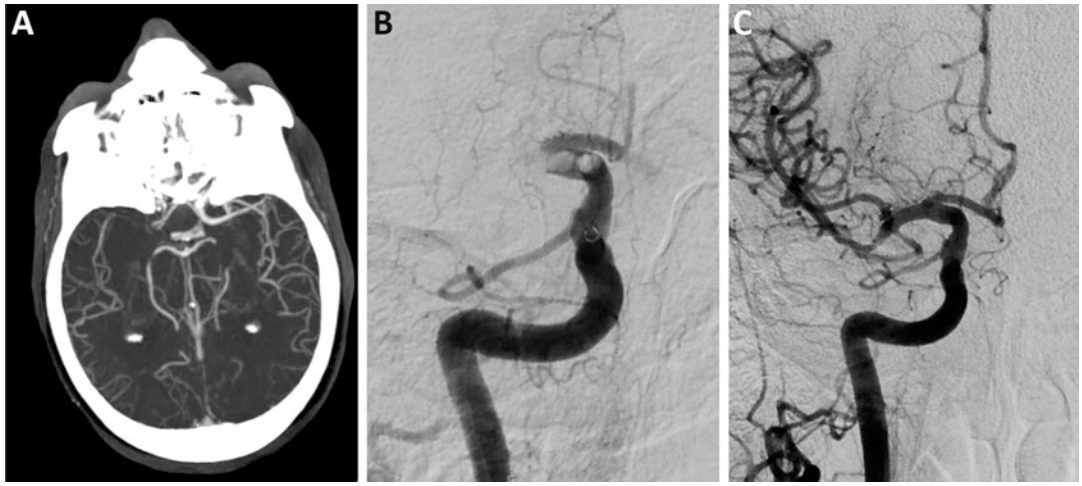

Fig. 8.2 CTA is highly accurate in identifying large vessel occlusion noninvasively in patients with hyperacute stroke, allowing selection for subsequent EVT. This patient presented with sudden-onset left-sided weakness, confusion, and neglect within 2 h of onset. (**a**) CTA demonstrated a right ICA terminus occlusion extending into the right M1 and A1 segments. (**b**) Angiography confirmed the presence of thrombus and subsequent mechanical thrombectomy resulted in (**c**) recanalization of the arteries and reperfusion of the right MCA and ACA territories

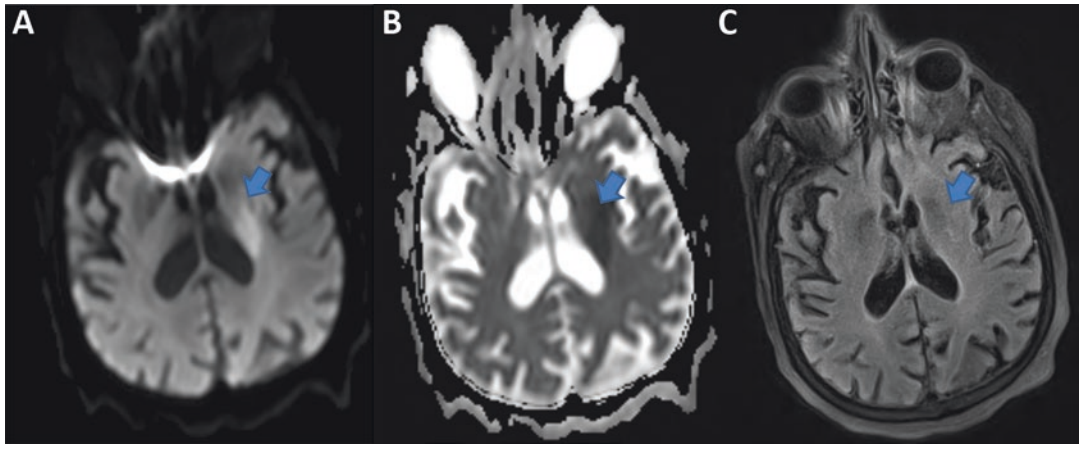

Fig. 8.3 MRI with diffusion-weighted imaging is highly sensitive to acute ischemic stroke. In this patient with sudden-onset right hemiparesis, (**a**) hyperintensity on a DWI sequence and (**b**) matching hypointensity on the ADC map confirm the presence of an acute or hyperacute infarct in the left corona radiata. (**c**) The absence of hyperintensity in this region on the FLAIR sequence suggests that this imaging was performed within 4–5 h of stroke onset. *ADC* apparent diffusion coefficient, *DWI* diffusion-weighted imaging, *FLAIR* fluid-attenuated inversion recovery

Suggested Imaging Protocols

There are many factors which determine the optimal imaging protocol, including the CT or MR scanner vendor, age, and equipment. The imaging protocol should also take into consideration patient motion and cooperation as well as technologist training and availability. The following represent imaging protocols that are reasonable for most Emergency Departments.

Noncontrast Head CT

- Spiral or conventional CT (the former may be better for moving patients, while the latter typically provides better gray-white matter differentiation).
- Volume of acquisition should include the vertex to the craniocervical junction, parallel to the inferior orbitomeatal line.
- kVp and mAs should be adjusted to provide sufficient gray-white matter differentiation with a radiation dose that is as low as reasonably achievable.
- 3–5 mm thick slices with 3–5 mm intervals, axial brain soft kernel reconstructions to evaluate for intracranial hemorrhage; note that 5 mm thick slices are preferred for ASPECTS rating, but thinner slices might be superior for subtle hemorrhage detection.
- Equivalent size axial bone kernel reconstructions.

CT Angiography

- Serum creatinine evaluation should not delay CTA in patients who are potential candidates for endovascular thrombectomy (as discussed in detail above).
- Spiral or helical CT is preferred, ideally on scanners with higher numbers of multidetector rows.
- Volume of acquisition should include the vertex to the aortic arch.
- kVp and mAs should be adjusted to provide sufficient vascular definition with a radiation dose that is as low as reasonably achievable.
- Bolus tracking from the aorta; if a single phase is obtained, an arterial-to-arteriovenous phase is preferred with the option to obtain a more delayed phase if needed.
- 1 mm thick slices with 0.5 mm intervals, soft tissue reconstructions to evaluate for large vessel occlusion.
- 10–30 mm MIPs in the axial and coronal planes to evaluate for large vessel occlusion.

Hyperacute Stroke MRI

Stroke MRI protocols vary greatly among institutions. The following protocol is reasonable to rapidly identify/confirm stroke, exclude hemorrhage, and evaluate for large vessel occlusion:

- MRI safety screening per institutional policy or skull, neck, and chest radiography if unable to obtain
- DWI and ADC map
- FLAIR sequence
- Blood-sensitive sequence (T2* or SWI)
- Time-of-flight noncontrast MRA to evaluate for large vessel occlusion

Future Research

Research in stroke imaging is advancing rapidly—so much that a portion of what is written here will almost certainly be outdated by the time of publication. Many important questions remain, such as the role of advanced penumbra and collateral imaging if any, more accurate determination of ischemic core using CT, whether imaging evaluation can be performed completely in the angiography suite with new tomographic techniques, methods to improve systems of stroke care beyond single hospitals to networks of hospitals, the applicability of any of this to pediatric stroke, and the applicability if any in underdeveloped nations where healthcare resources are severely limited. Cost-effectiveness analyses must now also be updated given the recent positive RCTs for endovascular thrombectomy and were therefore not discussed here. Finally, while intravenous thrombolysis 20 years ago and now endovascular thrombectomy represent revolutionary advances in the treatment of hyperacute ischemic stroke, many stroke patients remain disabled; developing effective imaging and treatment methods for these patients remains a critical goal for future research in stroke imaging.

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