Managing Patients With Transient Ischemic Attack

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Editor's Note: *The Expert Clinical Management series consists of shorter, practical review articles focused on the optimal approach to a specific sign, symptom, disease, procedure, technology, or other emergency department challenge. These articles—typically solicited from recognized experts in the subject area—will summarize the best available evidence relating to the topic while including practical recommendations where the evidence is incomplete or conflicting.*

INTRODUCTION

Approximately 300,000 patients are treated annually in US emergency departments (EDs) for cerebral transient ischemic attack.[1] Their management is variable.[1,2] Created in 1975, the historical definition[3]—focal neurologic symptoms with a vascular cause, lasting less than 24 hours—no longer makes sense in a world of magnetic resonance imaging (MRI), fibrinolytic treatment for ischemic stroke, and a better understanding of the ultraearly stroke risk after transient ischemic attack. The new definition of transient ischemic attack is "a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction."[4]

The last 2 decades have witnessed an explosion of important research about transient ischemic attack. Most studies on transient ischemic attack use the historical definition, and many combine patients with transient ischemic attack and minor ischemic stroke (usually defined as a stroke that leaves a patient without a significant, disabling deficit) because the clinical approach to diagnosis and treatment in both groups is identical.

Although most patients are asymptomatic at presentation and have normal physical examination results, transient ischemic attack is a neurologic emergency. The incidence of acute ischemic stroke within 48 hours of an ED visit for transient ischemic attack is 4.8% (182/3,814 patients; 95% confidence interval [CI] 4.0% to 5.6%).[5] Accumulating evidence shows that secondary stroke prevention—the rapid implementation of multiple interventions—reduces the outcome of stroke by as much as 80%.[6-9]

Because accurate diagnosis, rapid testing, and implementation of treatments can prevent disabling and fatal strokes, transient ischemic attack has enormous public health importance and risk-management significance. This article reviews the management of neurologically normal patients who receive a clinical diagnosis of a transient ischemic attack in the ED.

CLINICAL DIAGNOSIS

Patients with transient ischemic attack usually present with the abrupt onset of focal neurologic symptoms lasting less than 1 hour. In a study of 1,328 transient ischemic attack patients, the median duration was 14 minutes for carotid events and 8 minutes for vertebrobasilar events.[10] In another study of 382 patients, 60% of patients' symptoms resolved within 1 hour.[11] The diagnosis of transient ischemic attack is usually based entirely on the patient's history. Neurologic examination result is normal and no useful biomarkers exist. If neurologic findings persist, treat as stroke (Figure 1). Other conditions such as migraine, seizure, and peripheral vestibular conditions can mimic transient ischemic attack (Figure 2).[12-15]

Misdiagnosis in the ED is reportedly as high as 60%.[15] Factors associated with misdiagnosis are gradual onset, previous unexplained attacks of neurologic symptoms, and "nonspecific" symptoms.[15] In an ED study of 429 "transient ischemic attack" patients later evaluated by a neurologist, 41% received a discordant diagnosis, which was associated with presence of headache, involuntary movement, and dizziness.[16]

These studies are problematic for several reasons. First, the criterion standard in both was the final neurologist's diagnosis after incremental testing beyond the initial ED evaluation.[15,16] Second, interobserver agreement about transient ischemic attack diagnosis is poor even among stroke-trained neurologists.[17] Finally, some factors associated with misdiagnosis can be due to a transient ischemic attack.

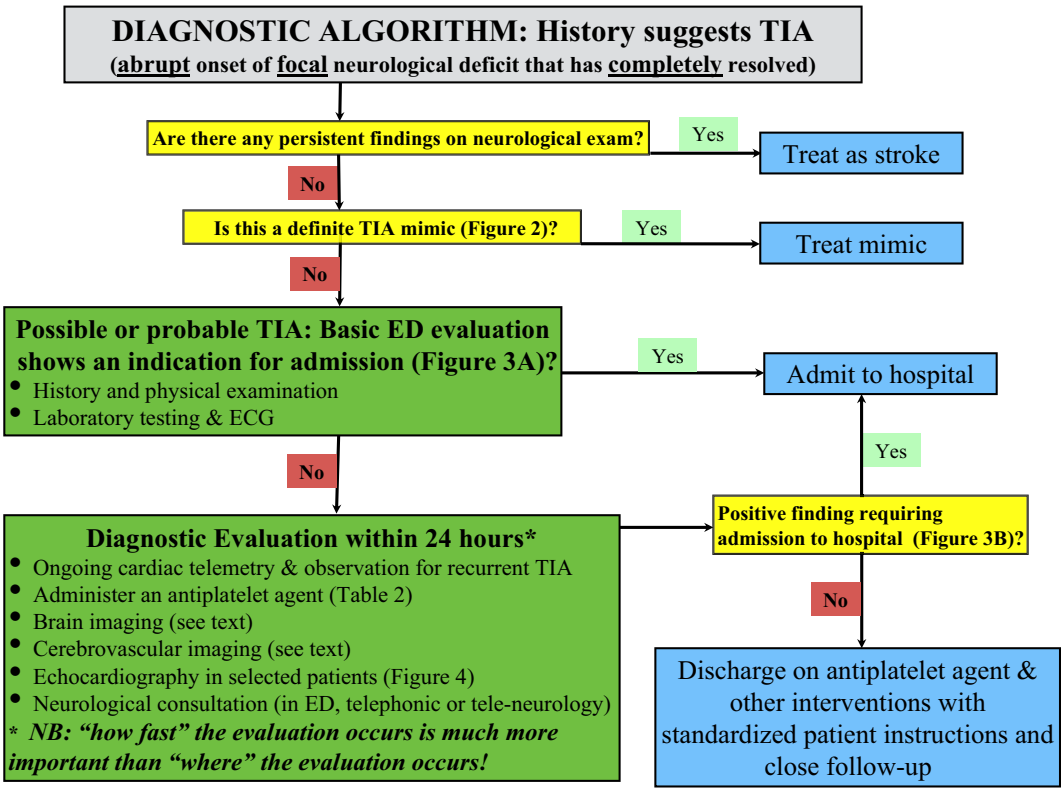

Figure 1. Diagnostic algorithm for patients with possible TIA. Patients discharged after having a TIA should be receiving an antiplatelet agent (unless clear contraindication), a statin, and antihypertensive medication if indicated. They should be given standardized instructions that address smoking cessation, weight loss, and the importance of close follow-up with their neurologist or primary care physician. If possible, arrange for application of long-term ambulatory cardiac monitoring. The timing of the follow-up will be determined in part by how much of the diagnostic evaluation was conducted in the ED or ED-based observation unit. *TIA*, Transient ischemic attack.

For example, involuntary movements are typical of limb-shaking transient ischemic attack, an uncommon but important variant that is almost always due to a high-grade internal carotid stenosis.[18] This is an exception to the otherwise useful maxim that transient ischemic attack (and stroke) generally present with "negative" symptoms, whereas diagnostic mimics (migraine and seizure) usually present with "positive" symptoms (Table 1).

Discounting episodic dizziness is also problematic.[19] Isolated episodes of vertigo accounted for half of the transient neurologic events that occurred in the 2 days preceding posterior circulation strokes,[20] often caused by vertebral stenosis.[21] Nonrotatory dizziness is the most common nonfocal symptom.[22] In another study of 1,850 patients with probable or definite transient ischemic attack, 177 (9.6%) had isolated atypical symptoms (eg, isolated diplopia, dysarthria, dizziness, sensory symptoms in a single limb or one side of the face).[23] Of the 177 patients, 18.1% had a major embolic source and 5.6% had high-grade arterial stenosis.[23] Posterior circulation transient ischemic attacks may have worse outcomes than anterior circulation ones.[24]

Alternatively, nonspecific symptoms of global cerebral hypoperfusion (eg, syncope, loss of consciousness), generalized weakness, vague lightheadedness, or altered mental status are rarely due to transient ischemic attack.[25] As a general rule, patients with abrupt onset and rapid offset of new localizable (to a specific artery) neurologic symptoms are considered to have experienced transient ischemic attack until proven otherwise. Symptoms that localize to the posterior circulation (eg, dizziness) often do not usually lateralize to one side of the body.

RISK STRATIFICATION

The first step in risk stratification is the initial evaluation. History, physical examination, and basic tests such as blood glucose level and ECG may identify high-risk patients (Figures 1 and 3).

The most commonly used formal risk-stratification tool, the ABCD2 scale, has been incorporated into American Heart Association guidelines for hospitalization of transient ischemic attack patients.[4] An American College of Emergency Physicians clinical policy recommends against using this score to identify safe-for-discharge patients.[26]

Stroke with transient symptoms

Seizure with postictal weakness

Complex migraine

Conversion reaction

Syncope

Peripheral vestibular processes (eg, Meniere's syndrome, BPPV, vestibular migraine)

Cranial neuropathy (eg, Bell's palsy, third nerve palsy)

Pressure-related peripheral neuropathy

Transient global amnesia

Metabolic conditions (eg, hypoglycemia, hyponatremia)

Figure 2. Differential diagnosis of transient ischemic attack.

This makes sense; although higher ABCD2 scores track with increasing stroke risk globally,[6] it has serious flaws when used for individual patients.

A prospective validation study from Canadian EDs of 2,056 patients with suspected transient ischemic attack reported that the enrolling physician's accuracy in calculating the ABCD2 score was poor (area under curve 0.56; 95% CI 0.47 to 0.65).[27] More important, the ABCD2 score does not accurately identify the very patients who are most important: those with large vessel stenosis and atrial fibrillation in whom specific, acute interventions prevent strokes.[28-30]

These problems with the ABCD2 score have led investigators to add imaging studies, including noncontrast brain computed tomography (CT), MRI including diffusion-weighted imaging, and various vascular studies, mostly carotid ultrasonography and CT angiography, to improve risk stratification. Diffusion-weighted imaging and cerebrovascular imaging predict short-term risk for stroke.[26,31]

Table 1. Examples of negative and positive neurologic symptoms.*

	Negative Symptom	Positive Symptom
Motor	Weakness	Involuntary movement (eg, shaking, seizure)
Sensory	Numbness or anesthesia	Tingling or dysesthesias
Visual	Blindness	Flashes of light or zigzag patterns

*Negative symptoms, in which the neurologic function is diminished or absent, are generally associated with ischemia or infarction. Positive symptoms, in which there is something present that is not usual, is generally associated with migraine or seizure phenomena.

A. ON INITIAL CLINICAL EVALUATION AND BASIC TESTING

Multiple, stuttering, or crescendo TIA presentation

TIA while receiving full anticoagulation

Severely abnormal vital signs

Relevant carotid bruit or cardiac murmur, prosthetic cardiac valve

Atrial fibrillation, other electrocardiographic findings suggesting a potential embolic source

Pregnancy

Logistic issues that interfere with an outpatient evaluation

Significant medical comorbidities making hospitalization a better option

B. FINDINGS FROM ADVANCED EVALUATION

Development of significant arrhythmia not found on initial ECG

Development of recurrent neurologic symptoms during evaluation

Infarction or other structural mimic found on brain imaging

Any large vessel atherosclerosis (intra- or extracranial) or other vascular lesions such as arterial dissection

If echocardiography is conducted, cardiac lesion requiring systemic anticoagulation

Figure 3. Findings that should prompt hospitalization.

However, in my opinion, risk stratification with MRI and vascular imaging is no longer "risk stratification" but simply performing the evaluation.[32] Conducting brain MRI and carotid artery imaging in a patient with suspected transient ischemic attack is similar to conducting chest CT angiography and bilateral leg ultrasonography to risk stratify patients with suspected pulmonary embolism.

DIAGNOSTIC TESTING

The goal of diagnostic testing is to identify treatable causes of the transient ischemic attack (Figure 3). All patients should receive basic laboratory testing, an ECG, and cardiac telemetry because atrial fibrillation accounts for approximately 20% to 25% of transient ischemic

attacks.[33,34] Even brief episodes of less than 30 seconds caught on monitoring may be significant.[35] For transient ischemic attack patients being discharged with no causal diagnosis found, consider arranging long-term ambulatory cardiac monitoring if possible.

All patients should have brain imaging, ideally MRI with diffusion-weighted imaging. Faster and easier to obtain, CT is an acceptable although inferior alternative. Structural transient ischemic attack mimics (eg, subdural hematoma, cerebral mass) are found in approximately 1% of neurologically intact patients.[36] Beyond diagnosing the occasional mimic, CT provides little value; diffusion-weighted imaging yields much more information, including evidence of infarction in a third of patients.[37] Positive diffusion-weighted imaging result is associated with increased recurrent stroke risk, but it does not drive treatment. The next diagnostic and therapeutic steps are identical in neurologically intact transient ischemic attack patients with or without a spot on MRI.[25] It is likely (but unproven) that diffusion-weighted imaging-positive patients could be safely discharged if the evaluation result for treatable causes is negative and secondary prevention strategies have been started.

The American College of Emergency Physicians policy recommends vascular imaging "when feasible," citing that there is no evidence that performing vascular imaging in the ED improves patient-centered outcomes.[26] I disagree with this recommendation; absence of evidence is not equivalent to evidence of absence. Vascular imaging is probably the single most important test.

First, it is almost always feasible to conduct CT angiography in ED patients. Second, large vessel disease is a major finding that drives acute treatments. Early identification of patients with symptomatic carotid stenosis greater than 50% confers a high risk for stroke that is reduced by urgent revascularization.[38] In one study of 312 patients, large vessel disease caused 10.6% of the transient ischemic attacks, but accounted for 40% of the recurrent neurologic events within 2 days (odds ratio 12; 95% CI 1.8 to 74.5).[39] Carotid ultrasonography is acceptable to detect internal carotid stenosis.[26] However, ultrasonography will not detect vertebral and intracranial artery stenoses, which also carry a high stroke risk.[20,40]

Even when stroke specialists evaluate transient ischemic attack patients, echocardiography is applied selectively (59% of 4,583 patients in one study in whom clinically relevant echocardiographic findings were found in less than 5%).[6] In another study of 869 transient ischemic attack patients, 60 of 603 (10%) who underwent echocardiography (mostly transthoracic) had a positive finding.[41] However, new anticoagulation was started in accordance with the echocardiographic result in only 15 patients (2.5% of the 603).[41] Figure 4 lists criteria to help select which transient ischemic attack patients may benefit from echocardiography.

- Patients without an otherwise indication for full anticoagulation (such as atrial fibrillation)
- No other cause found on initial evaluation (eg, atrial fibrillation, carotid stenosis) or suspected small vessel disease
- Multiple areas of infarction on MRI (suggesting an embolic cause)
- Younger age (<55 y) without another cause found
- Suspected or known cardioembolic source on clinical evaluation (heart murmur or prosthetic valve, heart failure or known LV dysfunction, chest pain, abnormal ECG result other than atrial fibrillation) or known abnormal previous echocardiography result

Figure 4. Transient ischemic attack patients who may benefit from echocardiography. *LV*, Left ventricular.

TREATMENT AND DISPOSITION

Emergency evaluation and implementation of treatments significantly reduces acute stroke risk.[6-9] Use of anticoagulation for cardioembolic transient ischemic attack and revascularization for carotid disease account for only a proportion of this reduction. Antiplatelet treatment, statin administration, blood pressure reduction, smoking cessation, and other measures are also important.[42]

The vast literature on antiplatelet treatment in transient ischemic attack can be boiled down to a simple recommendation: unless there is a contraindication, give aspirin.[42] Table 2 lists alternative antiplatelet strategies.[42]

Pooled individual patient-level data from 15,778 transient ischemic attack and stroke patients randomized to aspirin versus control demonstrated that aspirin reduces stroke risk far better than previous studies have reported.[43] Reduction of fatal and disabling strokes was 70%, with a negative hazard ratio of 0.29 (95% CI 0.20 to 0.41).[43] The reduction was the greatest in patients whose qualifying event was transient ischemic attack or minor ischemic stroke (N=12,417), for whom the negative hazard ratio for stroke reduction within 2 weeks was even better: 0.07 (95% CI 0.02 to 0.31).[43] Given this degree of risk reduction, some international experts have begun giving aspirin before brain imaging (to exclude hemorrhage) (personal communication, Peter Rothwell,

Table 2. ED-relevant American Heart Association recommendations for antiplatelet treatment (modified from 2014 American Heart Association recommendations).

Recommendation (Class/Level of Evidence)	Comments
For patients with noncardioembolic TIA, the use of antiplatelet agents rather than oral anticoagulation is recommended (I-A)	
Aspirin (50–325 mg/day) monotherapy (1-A) or combination aspirin 25 mg/extended-release dipyridamole 200 mg twice daily (I-B) is indicated as initial therapy	According to evidence, aspirin is still the simplest effective agent to give
Clopidogrel (75 mg) monotherapy is a reasonable option in place of aspirin or aspirin/dipyridamole (IIa-B)	Probably the best strategy in aspirin-allergic patients
Individualize antiplatelet agent according to patient risk-factor profiles, cost, tolerance, efficacy, and other clinical characteristics (I-C)	
The combination of aspirin/clopidogrel might be considered for initiation within 24 h of a TIA and continued for 90 days (IIB-B)	
For patients who have a TIA while receiving aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although additional antiplatelet agents are often considered, no single agent or combination has been adequately studied in patients who have been receiving aspirin (IIb-C).	

University of Oxford, May 2017; personal communication, Philippa Lavallee, HU-Paris Nord, May 2017). Although unstudied, this strategy is likely safe and effective and would also encourage substituting the quick but rarely useful CT with the slower-to-obtain but far more informative MRI.

Admit transient ischemic attack patients with a cardioembolic cause. Most transient ischemic attack patients with atrial fibrillation should receive full anticoagulation.[42] The choice of agent—warfarin versus one of the newer oral agents—ideally should be made in consultation with the physician who will follow the patient long term or standardized at each institution to avoid long delays. Other cardioembolic sources include cardiomyopathy, left ventricular thrombus, valvular disease without atrial fibrillation, and aortic arch atherosclerosis.

Admit patients with large vessel disease. Patients with carotid stenosis should receive aspirin and have urgent neurologic consultation. Depending on patients' age, sex, degree of stenosis, and symptoms, many will benefit from carotid revascularization.[44] Endarterectomy is most effective in older male patients with greater than 70% stenosis and when conducted within 2 weeks of the transient ischemic attack.[45,46]

Patients with other large vessel disease, such as vertebral or intracranial artery stenosis or arterial dissections, should all receive aspirin, have neurology consultation, and be admitted. For vertebral artery disease, stenting and surgical techniques are rapidly evolving.[42] For intracranial large vessel lesions, the data for procedural interventions are less compelling,[42] but these patients have an especially high early stroke risk.[31,40]

Where should all of this initial evaluation occur? Traditionally, the outpatient setting (slow and inefficient) and hospitalization (expensive and inefficient) were used. Increased recognition of the short-term stroke risk has led to various alternative models of care, including the ED, ED-based observation units, and same-day specialty-run outpatient transient ischemic attack clinics.[47] In most EDs, giving aspirin and performing basic testing plus brain and cerebrovascular imaging can be accomplished within hours. The ED-based observation unit is another efficient model and allows more time for a complete evaluation and consultation.[9,48]

The reality is that emergency physicians must use whatever system of care is available to them. Whatever that is, it is important to recognize that how fast the evaluation occurs is much more important than where it occurs.[25,32,49] Rapid use of antiplatelet treatment and other measures discussed above will prevent disabling and fatal strokes in many of these patients.

Patients discharged from the ED or ED-based observation unit should receive standardized instructions about neurologic symptoms for which to immediately return, information about lifestyle changes, and information about various medical interventions, along with a tight follow-up ideally with a stroke neurologist, with the recognition that this is not possible in some settings. Emergency physicians should collaborate with physicians from other stakeholder specialties to create the most streamlined infrastructure that their local environment will support to evaluate patients with transient ischemic attack.

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