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REVIEW - NARRATIVE

CME

Management of Ischemic Stroke: Part 2. The Inpatient Stay

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BACKGROUND: Acute ischemic stroke is commonly encountered by the hospitalist. There have been dramatic changes in our ability to care for these patients both acutely and in secondary prevention. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) primary stroke center certification has become progressively more important to institutions nationally and emphasizes many elements of the inpatient stay and discharge process.
PURPOSE: After admission, the focus changes to avoidance of complications and the appropriate initiation of allied therapies and secondary prevention.
DATA SOURCES: Primary trials, current guidelines.
CONCLUSIONS: The hospitalist is well-positioned to play a major role in the treatment of stroke patients as well as the systems work that aids in the management of this population. ***Journal of Hospital Medicine*** **2010;5:88–93.** © *2010 Society of Hospital Medicine.*

KEYWORDS: cerebrovascular disorders, guidelines, inpatient, stroke.

Inpatient stroke management includes many elements of care, at least as important as the initial portion of the patient's stay, as reviewed in part 1 of this article. The extent of further diagnostic evaluation varies widely depending on apparent risk factors on presentation. Likewise, further therapy, both inpatient and secondary prevention is based on identification of stroke mechanism. Hospitalists are uniquely positioned to have a tremendous impact on both stroke care and the prevention of recurrent disease.

Case Presentation

A 76-year-old right-handed male with a history of hyperlipidemia and myocardial infarction was found at 7 AM with right-sided paralysis and poor responsiveness on the morning of admission. Upon arrival to the emergency department (ED), with symptoms of partial aphasia, right hemiplegia, and left gaze preference, there was a high suspicion for a left middle cerebral artery (MCA) stroke. Unfortunately, he was excluded from receiving intravenous (IV) tissue plasminogen activator (tPA) or any other acute interventions as the last time he was known to be neurologically intact was the prior evening, which is taken to be the time of onset. Antiplatelet therapy was continued, and the patient admitted for further workup.

Inpatient Care

When an acute ischemic stroke patient is admitted to the hospital, he or she should be placed on a standardized acute stroke protocol (also known as (a.k.a.) a care map, order set, clinical pathway)—commonly created by a hospitalist/neurologist and a multidisciplinary team and admitted to a stroke unit. A stroke unit can take many forms, either as a physically separate unit in hospitals with sufficient volume or a floor where a lower volume of stroke patients are always admitted. Multidisciplinary care providers in the stroke unit have special training in stroke, and strong evidence from randomized trials shows that patients cared for in these units have significantly decreased mortality with improved functional outcomes.[1] Essentials of the stroke protocol or order set include cardiac telemetry, maintaining euthermia and euglycemia, closely following blood pressure and neurologic status, actively avoiding complications, initiation of secondary prevention treatment, early involvement of rehabilitation services, and patient education.

Euthermia may be assisted by administering scheduled Tylenol to the patient for the first 48 hours, but is not strictly evidence-based.[2] Though euthermia and euglycemia have not been shown to improve outcomes in acute stroke, studies have shown that hyperthermia and hyperglycemia are associated with worsened outcomes for patients with acute strokes.[3–5]

Blood Pressure Management

Normally, cerebral vascular autoregulation leads to stable cerebral blood flow over a range of systemic blood pressures. In the setting of an acute stroke, the ability to

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TABLE 1. Harmonized Acute Inpatient Stroke Care Performance Measures

Performance measure*	Definition*
1. DVT prophylaxis†	Patients who are nonambulatory should start receiving DVT prophylaxis by end of hospital day 2 (can be either compression devices or any low-dose heparin)
2. Discharged on antithrombotic therapy	Antiplatelet agent(s) or warfarin anticoagulation
3. Patients with atrial fibrillation receiving anticoagulation therapy	A proven approach to secondary prevention in such patients; practice at Harborview varies time of warfarin initiation based on infarct size with larger infarcts waiting up to 2 weeks before initiating warfarin (the best randomized trial showed no benefit for full-dose low-molecular-weight heparin over aspirin in the first 2 weeks)[50]
4. Thrombolytic therapy administered	In ischemic stroke patients who arrive at the hospital within 120 minutes (2 hours) of time last known well, for whom IV tPA was initiated at this hospital within 180 minutes (3 hours) of time last known well, and who qualify under strict criteria
5. Antithrombotic therapy by end of hospital day 2	Usually just antiplatelet agents, a minimal standard of care for ischemic stroke patients; should be started as early as possible, usually in ER
6. Discharged on statin medication	If LDL >100, or not measured or if on a statin drug prior to admission; to reduce risk of subsequent ischemic stroke
7. Dysphagia screening†	Prior to *any* PO food, fluids or medications; to reduce the chances of aspiration pneumonia
8. Stroke education†	Including for families if patient unable to participate, must include "personal risk factors for stroke, warning signs for stroke, activation of emergency medical system, need for follow-up after discharge, and medications prescribed"
9. Smoking cessation/advice/counseling†	For any patient who has smoked in the last year
10. Assessed for rehabilitation†	Or received therapy services; to facilitate progress to an optimal function outcome

NOTE: Active January 1, 2008.

Abbreviations: DVT, deep vein thrombosis; ER, emergency room; IV, intravenous; LDL, low-density lipoprotein; PO, by mouth; tPA, tissue plasminogen activator.

*Available at: http://www.jointcommission.org/CertificationPrograms/PrimaryStrokeCenters/stroke_pm_edition_2_ver_2a.htm.

†Applies to both ischemic and hemorrhagic stroke types; if not so marked, only applies to ischemic stroke patients.

autoregulate is diminished or absent in regions of and surrounding an acute ischemic stroke; as the area becomes ischemic, autoregulation opens the local vasculature maximally in an effort to drawn in as much blood as possible. Maximally dilated arterioles are perfused in direct correlation with systemic blood pressure, thus any drop in the systemic blood pressure leads to direct decreases in blood flow specifically in the area of ischemia; if there is a penumbra of marginally perfused tissue, such systemic blood pressure drops risk extending the area of fatal ischemia (increasing the size of the ischemic stroke).[6–8] Thus in the acute period of an ischemic stroke, the American Heart Association (AHA)/American Stroke Association (ASA) "Guidelines for the Early Management of Adults With Ischemic Stroke" (referred to herein as the "Guidelines")[10] suggest avoid treatment unless systolic blood pressures are >220 or diastolic pressures >105, and review the evidence to support this recommendation (p. 1671–1672). Those patients who receive tPA have a more stringent blood pressure threshold given their risk of intracranial hemorrhage; systolic blood pressures are accepted up to 180 prior to recommending treatment.

Higher-quality Inpatient Stroke Care and Harmonized Performance Measures

Beginning in January 2008, a set of 10 performance measures (Table 1) for inpatient acute stroke care have been agreed upon ("harmonized") by 3 major stakeholders including the Joint Commission, the ASA's "Get with the Guidelines–Stroke" quality improvement program, and the Center for Disease Control and Prevention's (CDC's) Paul Coverdell Acute stroke registries. These performance measures were selected to help avoid complications (deep vein thrombosis [DVT], aspiration pneumonia), encourage appropriately aggressive care (tPA administration), optimize secondary prevention (antithrombotics, cholesterol lowering, smoking cessation, education), and facilitate functional recovery (early rehabilitation). All 10 measures are appropriate for consideration in every ischemic stroke patient, and 5 are appropriate for the hemorrhagic stroke types.

Further Workup

After the ischemic stroke patient has had their computed tomography (CT) scan, possibly a computed tomography angiography (CTA), been admitted to the stroke unit, started on an antithrombotic medication, and had their blood pressure appropriately treated, attention then turns to defining the pathophysiology related to the stroke and starting an optimal regimen for secondary prevention. Imaging of the cerebral vasculature including both extracranial and intracranial large vessels is a vital first step in understanding the cause of ischemic stroke. There are multiple potential modalities (magnetic resonance angiography [MRA], CTA, and duplex/transcranial Doppler), the choice of which depends on local availability and expertise as well as the specific clinical situation. Magnetic resonance imaging (MRI) of the brain for all ischemic stroke patients is standard of care at most stroke centers; per the "Guidelines," "MRI is better at distinguishing acute, small cortical, small deep, and posterior fossa infarcts; at distinguishing acute from chronic ischemia; and at identifying subclinical satellite ischemic lesions that provide information on stroke mechanism" (p. 1668). New techniques including magnetic resonance (MR) and CT perfusion scanning can show the ischemic region in the acute setting and may one day help select patients for

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specific therapies, but are not yet widely available nor have they been shown to alter outcomes.

An electrocardiogram is indicated for all stroke patients, as is admission to a cardiac telemetry bed for at least 24 hours to document any arrhythmias, the most common being atrial fibrillation ("Guidelines," p. 1666, 1673). An echocardiographic study (ECHO) of the heart with bubble study should be performed in most cases (although which cases may specifically benefit is unclear) to identify a cardioembolic source for the stroke, such as low cardiac ejection fraction, atrial septal aneurysm, patent foramen ovale (PFO), or a cardiac thrombus. The bubble study increases the sensitivity of detecting a PFO, which could serve as a gateway for venous embolization to the cerebral arteries. Assuming a large PFO is discovered, other studies such as lower extremity Doppler may be warranted to investigate other potential sources of thrombi (ie, DVT).

Regarding laboratory testing, fasting lipids should be checked as hyperlipidemia is a common modifiable risk factor for ischemic stroke. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial included ischemic stroke patients that had low-density lipoprotein (LDL) cholesterol between 100 mg/dL and 190 mg/dL and randomized them to receive atorvastatin 80 mg/day vs. placebo. Results showed a 16% relative risk reduction in recurrent stroke; however, there was a small increased risk of intracranial hemorrhage.[9] As shown in Table 1, use of a statin on discharge is now a national performance measure for ischemic stroke.

Dissection is a common cause of stroke in young patients without traditional risk factors. Other serologies, such as hypercoagulable studies, may be warranted in patients with no other risk factors for strokes, paradoxical embolus, or of young age (eg, 45 years and under). The arterial hypercoagulable panel consists of antiphospholipid antibody panel, homocysteine levels, lupus anticoagulant levels, and prothrombin time/partial thromboplastin time (PT/PTT). The venous hypercoagulable panel consists of the laboratory values checked, with the arterial hypercoagulable and activated protein C (APC) resistance, Factor VIII activity, Factor II DNA, Factor V DNA if the APC resistance is positive, antithrombin III activity, and activity of proteins C and S. If a patient is found to have a hypercoagulable state, long-term therapy often involves careful consideration of the choice of antiplatelet therapy vs. anticoagulation with warfarin.[10]

Initiating Secondary Prevention

Upon admission, the clinician faces a variety of treatment choices for secondary stroke prevention. The proper choice depends on the results of the workup and the presumptive pathophysiology.

Noncardioembolic/Atherothrombotic/Lacunar

The Antithrombotic Trialists' Collaboration meta-analysis found that patients with a prior stroke or transient ischemic attack (TIA) had a highly significant decrease in the rate of subsequent vascular events (over about 3 years) on antiplatelet therapy (17.8% vs. 21.4%, $P < 0.0001$) and were unable to find a significant difference between low-dose and high-dose aspirin for secondary prevention.[11] Thus, it is reasonable to place an acute stroke patient naive to antithrombotic therapy on 81 mg of aspirin or 325 mg for long-term prevention (325 mg is specifically recommended in the acute setting). Several studies such as the WARSS and ESPRIT trials have shown antiplatelet agents to be at least as effective as anticoagulation in noncardioembolic ischemic strokes.[12,13] Guidelines from Europe, the American College of Chest Physicians, and the AHA/ASA all state it is acceptable to choose either aspirin monotherapy, aspirin/extended release dipyridamole combination therapy, or clopidogrel monotherapy as first-line agents for long-term secondary prevention in noncardioembolic ischemic stroke.[14–16] There is no clear evidence that patients who suffer an ischemic stroke while on aspirin will derive additional benefit from increasing the aspirin dose. The newer guidelines go on to recommend aspirin/extended release dipyridamole (ER-DP) combination therapy or clopidogrel monotherapy over aspirin monotherapy, the former with a stronger level of recommendation based on the results of 2 randomized trials. These recommendations were all published without knowledge of the results of the Prevention Regimen For Effectively Avoiding Second Strokes (PRoFESS) study, which directly compared aspirin/extended release dipyridamole combination therapy to clopidogrel monotherapy for long-term secondary prevention. The rate of first recurrent stroke was not significantly different between the 2 therapies (9.0% ER-DP plus aspirin, 8.8% clopidogrel; hazard ratio [HR], 1.01; 95% confidence interval [CI], 0.92–1.11). Other outcomes also showed few differences, although there were more major hemorrhagic events in the ER-DP plus aspirin group (4.1% vs. 3.6%; HR, 1.15; 95% CI, 1.00–1.32; $P = 0.06$).[17]

The ASA Stroke Prevention Guideline from 2006 states, with continued relevance, "The selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, tolerance, and other clinical characteristics."[10] Of note, both the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) and Management of ATherothrombosis with Clopidogrel in High-risk patients with recent TIA or ischemic stroke (MATCH) trials found a significant increased risk for hemorrhage complications with long-term use of the aspirin and clopidogrel combination,[18,19] and the 2008 update to the ASA Stroke prevention guidelines state that "the addition of aspirin to clopidogrel increases the risk of hemorrhage. Combination therapy of aspirin and clopidogrel is not routinely recommended for ischemic stroke or TIA patients unless they have a specific indication for this therapy (i.e., coronary stent or acute coronary syndrome)."[15]

Atrial Fibrillation

Though our case patient did not have atrial fibrillation, this condition does deserve mention. About 15% to 20% of

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ischemic stroke patients have atrial fibrillation. The overall risk for stroke in patients with atrial fibrillation is about 5% per year; however, patients who have a history of stroke increase their risk factors for subsequent strokes to about 12% per year. In most cases, anticoagulation has proven to be the superior agent for primary and secondary stroke prevention with warfarin reducing the risk by 67% compared to aspirin, which only reduces the risk of stroke by 20%. A meta-analysis from 2002 showed that patients who had a prior stroke or TIA decrease their risk of subsequent strokes to 4%/year on oral anticoagulation therapy, resulting in an 8% absolute risk reduction. Patients on aspirin therapy only decrease their risk to 10%/year, or a 2% reduction in stroke events.[20] Unless there is a strong contraindication (eg, bleeding diathesis, history of life threatening gastrointestinal [GI] bleeding, history of fall with subdural hematoma, etc.), virtually all ischemic stroke patients with atrial fibrillation should be anticoagulated for life. Anticoagulation in the setting of atrial fibrillation is seriously underutilized.[21] The highest quality study on early anticoagulation for ischemic stroke associated with atrial fibrillation suggested that there was no benefit to starting anticoagulation earlier than 2 weeks after a stroke, and there may actually be a higher complication rate (compared to aspirin).[22] Other cardiac indications for anticoagulation include left ventricular thrombus and mechanical valves.

Carotid Stenosis

Significant ipsilateral stenosis of the internal carotid artery in a patient with ischemic stroke is a strong indication for intervention, usually a standard carotid endarterectomy (CEA). Stenosis of 70% to 99% is the strongest indication for CEA, and may be of greatest benefit in men, those 75+ years of age, and if surgery is done <2 weeks after the most recent symptoms.[23] In patients with minor stroke or TIA, recent recommendations and our practice is to admit to the hospital and perform endarterectomy as soon as possible (those with major stroke may have a greater risk of complications with early CEA).[24] Stenting should only be considered instead of CEA if high risk (for surgical complications) criteria are present. These high risk criteria include patients having "significant comorbidities and/or anatomic risk factors (ie, recurrent stenosis and/or previous radical neck dissection), and [who] would be poor candidates for CEA in the opinion of a surgeon."[25] For stenoses of 50% to 69%, intervention is not as compelling, and decisions should be individualized based on patient characteristics; in this group, stenting should only be considered in the setting of a clinical trial or if an investigational device exemption (IDE) exists at your institution.[26]

Dissection of the Carotid or Vertebral Arteries

This is a common cause of stroke in younger adults. It should be suspected in patients without other clear causes of stroke and significant disease of the extracranial arteries. Diagnosis can usually be made with CTA or MRA, though it is suggested that the best modality may be "T_1-fat-saturated" MRI images of the neck. Debate exists as to the best approach to treatment of dissections due to the absence of randomized trials. A recent comprehensive review suggested anticoagulation for 3 to 6 months followed by indefinite antiplatelet therapy for symptomatic dissections and antiplatelet therapy alone for asymptomatic dissections.[27]

PFO-related Stroke

If the patient is found to have a PFO, its role in comparison to traditional risk factors must be weighed carefully. Epidemiological studies suggest that PFO may be most relevant in younger patients, those with cryptogenic stroke (no obvious cause and lack of traditional risk factors), those with higher risk associations including interatrial septal aneurysm, larger PFOs or history of previous cryptogenic stroke.[28,29] The best medical therapy for seemingly PFO-related ischemic stroke is also unclear; a reasonable approach might be aspirin if neither high-risk associations nor a hypercoagulable state is present, and warfarin if either are present. Transcatheter closure of PFO is approved by the U.S. Food and Drug Administration (FDA) only under an IDE for patients who have had a recurrent event on maximally tolerated medical treatment, and requires approval from the human research committee (internal review board [IRB]) at your hospital. It is not known if closure is superior or inferior to best medical therapy, and a practice parameter from the American Academy of Neurology strongly encourages appropriate patients to consider participation in ongoing randomized trials.[28] Further information on these trials is available at: http://www.amplatzer.com/US/Respect and http://www.closurei.com/physician.

Our patient underwent a CTA of the head and neck in the emergency room to see if he would be a candidate for other interventions; unfortunately, he did not meet the time criteria. CTA showed complete occlusion of the left internal carotid artery at the bifurcation with heterogeneous retrograde filling (Supporting Figure 1). Complete occlusion of the proximal third of the left M1 segment was also seen with relative oligemia in the left MCA distribution, though several small peripheral M3/M4 vessels were opacified in the territory indicating collateralization (Supporting Figure 2). A MRI showed a large area of diffusion-weighted abnormality (Figure 1). Interestingly, the patient's transthoracic echocardiography (TTE), which did not show evidence of a PFO, did reveal a calcified thrombus in the left ventricle. Though no arrhythmias were captured on telemetry, this thrombus does serve as a potential source of cardioembolic emboli to the cerebral vasculature. It was felt that the most likely source of the patient's acute infarct was from artery-to-artery emboli from his internal carotid occlusion given the infarct location and the lack of infarction in other vascular distributions (as one might see from a cardiac embolic source). Therefore, his medical management consisted of an

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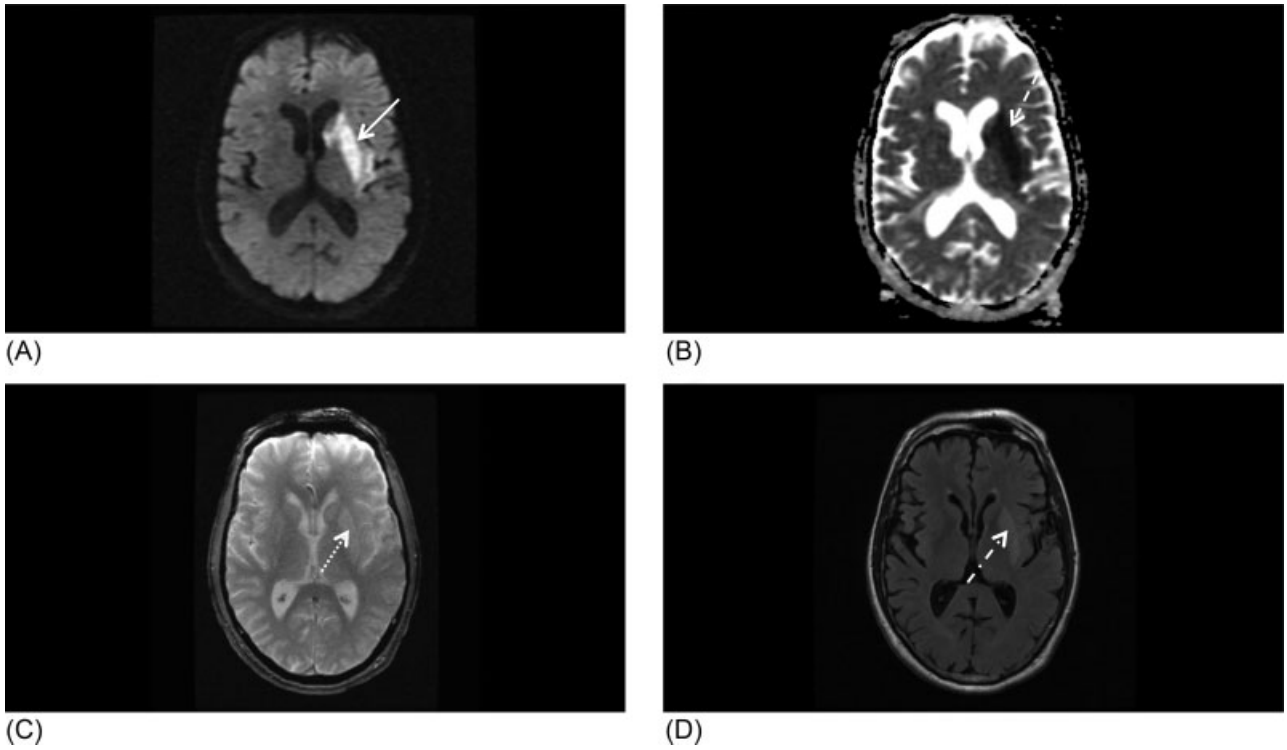

FIGURE 1. MRI image of brain without contrast. (A) Diffusion-weighted image in left MCA distribution (solid arrow). (B) ADC map corresponding to areas of restricted diffusion positivity (dashed arrow). (C) Gradient recalled-echo (GRE) image showing no evidence of hemorrhagic conversion, which would appear black on the film (dotted arrow). (D) Fluid attenuation inversion recovery (FLAIR) image indicating that the stroke is >24 hours old (dashed dotted arrow).

antiplatelet regimen for 2 weeks followed by a transition to warfarin alone 2 weeks after his acute infarct as secondary stroke prevention due to the cardiac thrombus. Given the complete occlusion of the internal carotid artery and M1 segment, there was concern that the penumbra might be at risk of infarction (supporting standard guidelines of permissive hypertension). By the end of his hospitalization, the patient had improved and was transferred to inpatient rehabilitation.

The guidelines for acute stroke management continue to rapidly evolve. Certainly, there are effective treatments for acute ischemic stroke, with variation based on the timing of patient arrival at the hospital, the underlying pathophysiology, and the treatment capabilities of the individual hospital. Secondary stroke prevention is extremely important and has been emphasized during inpatient admissions with the establishment of an appropriate medication regime, given that patients are more likely to stay on treatment that is initiated around the time of a diagnosis.[29] Evidence strongly suggests that management of acute stroke is improved by an organized approach to care, including the expertise of a multidisciplinary team in a specialized stroke unit. Hospitals committed to high quality of care for acute stroke patients should strongly consider the Joint Commission certification process or an analogous local certification. Such certification demonstrates a hospital's commitment to providing high-quality care, what every stroke patient wants and deserves.

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