AHC Media LLC

Rapid Reference Card Enclosed

CME evaluation included with this issue.

The Practical Journal for Emergency Physicians

Emergency Medicine Reports®

Volume 28, Number 26

December 10, 2007

I trained during the era when the prevailing approach for patients with acute strokes was to define the area of brain affected using only clinical examination, exclude treatable intracranial hematoma (without CT!), and to admit the patient for a period of observation and initiation of physical rehabilitation. With the exception of possibly using heparin for crescendo TIAs, there was a nihilistic attitude about stroke treatment. Now we have prehospital stroke triage criteria, primary stroke centers, acute stroke teams, and more imaging technologies than I can remember. In addition, we are discovering more causes for acute strokes, especially in younger patients. This manuscript reviews these causes, their assessment, and management. After reading this, I suspect many will revise their acute stroke protocols and order sets to consider these possibilities in younger patients.

—J. Stephan Stapczynski, MD, FACEP, Editor

Stroke in Young People: A Different Differential

Authors: **Susan P. Torrey, MD, FACEP**, Associate Residency Director, Department of Emergency Medicine, Baystate Medical Center, Springfield, MA; and **Tala Elia, MD**, Attending Physician, Department of Emergency Medicine, Baystate Medical Center, Tufts University School of Medicine, Springfield, MA.

Peer Reviewers: **Jonathan Glauser, MD, FACEP**, Chairman, Emergency Department, Cleveland Clinic, Cleveland, OH; and **Steven M. Winograd, MD, FACEP**, Attending Physician, Emergency Department, Horton Hospital and Arden Hill Hospital, Orange County, NY.

While stroke is most often a result of progressive atherosclerotic cerebrovascular disease, occurring with increasing frequency as the population ages, there are less common causes of stroke that mainly affect younger populations. These alternative etiologies of stroke symptoms require an emergency physician to have a broader differential diagnosis of acute focal neurologic symptoms in a young population, and sufficient knowledge to facilitate an appropriate evaluation and treatment plan. The differential diagnosis of stroke in young people (usually defined as younger than 45 years) includes dissection of cerebrovascular arteries; thrombosis of cerebral veins and venous sinuses; embolism in general, and paradoxical embolization via a

Statement of Financial Disclosure

To reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Farel (CME question reviewer) owns stock in Johnson & Johnson. Dr. Elia (author) serves as a speaker for Sonoran Ultrasound, an ultrasound education company. Dr. Torrey (author), Dr. Glauser (peer reviewer), Dr. Winograd (peer reviewer), Dr. Schneider (editor), and Dr. Stapczynski (editor) report no relationships with companies related to the field of study covered by this CME activity.

patent foramen ovale in particular; some causes of intracerebral hemorrhage; and a list of unique causes.

Epidemiology

Epidemiologic studies of strokes in young adults have been limited by population studies that use highly variable diagnostic criteria and evaluation protocols. Given these limitations, it remains common to find many of these patients with no specific etiology for their ischemic stroke, hence the term "cryptogenic stroke" which has come into popular use in the last decade. A review of population-based articles[1-5] finds that strokes in young people (under the age of 45) have an incidence of 10-34 cases per 100,000 population per year. Of these, the most common etiologies include premature atherosclerotic vascular disease (7-11%), hematologic disorders inducing thrombophilia (7%), cervical artery dissection (8-20%), cardioembolic (6-33%), and cryptogenic stroke (21-60%). Unlike older patients diagnosed with ischemic stroke, younger patients generally have little to no risk factors for atherosclerotic disease. Diagnostic testing for vascular disease tends to be unremarkable and does not reveal the cause of the cerebral infarct in the vast majority of young adult patients. Up to 43% of young adults with ischemic strokes have no identifiable cause and are classified as "cryptogenic strokes."

Table 1. Causes and Incidence of Stroke in Young People

CAUSES OF STROKE IN YOUNG PEOPLE	%
Premature atherosclerotic disease	7–11
Cardioembolism, including PFO	6–33
Dissection of cervicocerebral arteries	8–20
Hematologic issues, including thrombophilia	7–10
Rare causes, including migraine, sickle cell, etc.	8–30
Unknown (cryptogenic)	21–60

Not surprisingly, the study with the lowest number of cryptogenic strokes had the most rigorous diagnostic plan, including liberal use of CT and MRI with angiographic evaluation of carotid arteries and posterior circulation, as well as frequent transesophageal echocardiography.[1]

Patent Foramen Ovale

The high rates of cryptogenic stroke in young, seemingly healthy adults have led to investigations for other causes of stroke beyond vascular and atherosclerotic disease. One strong association that has emerged is the relationship between cryptogenic strokes and a patent foramen ovale (PFO). A PFO is a remnant of fetal circulation that results from the failure of the primum and secundum septa to fuse. The prevalence of PFOs in the general population is as high as 27%, affecting men and women equally.[6] Patients younger than 55 years old with a cryptogenic stroke have an associate with PFO six times greater than a control population, leading to the hypothesis that a PFO may play a role in the cause of stroke in these patients.[7]

The proposed mechanism for the involvement of PFOs in stroke is by migration of a thrombus from the venous circulation to the right atrium. The clot is then shunted to the left atrium via the PFO and from there embolizes systemically.[8] This phenomenon is also known as a "paradoxical emboli" and occurs when right atrial pressure exceeds left atrial pressure. In a patient with normal cardiovascular function, this right to left shunt can be transient during normal respiration or after the release of Valsalva maneuvers such as straining or coughing. Fourteen percent of asymptomatic patients with a PFO have a right to left shunt at rest. That number increases to 23% with Valsalva maneuvers.[9] Despite this, patients with cryptogenic stroke and PFO rarely report symptom onset after valsalva maneuvers. Other causes of a right to left shunt include acute pulmonary embolism, which causes pulmonary hypertension, as well as right ventricular infarct and acute respiratory failure.[8] One study even reports an incidence of paradoxical embolism as high as 60% in patients with pulmonary embolism.[10] Therefore, when confronted with an ischemic stroke in a young adult in which a paradoxical embolism is suspected, consideration should be given to determine if an identifiable embolic source or precipitating factors exist. However, in most patients the source of thrombus remains unidentified despite diagnostic testing.

Several factors are thought to increase the risk of stroke in patients with a PFO. These include a large opening, a large right

Emergency Medicine Reports™ (ISSN 0746-2506) is published biweekly by AHC Media LLC, 3525 Piedmont Road, N.E., Six Piedmont Center, Suite 400, Atlanta, GA 30305. Telephone: (800) 688-2421 or (404) 262-7436.

Senior Vice President/Group Publisher: Brenda Mooney
Associate Publisher: Lee Landenberger
Specialty Editor: Shelly Morrow Mark
Marketing Manager: Shawn DeMario
GST Registration No.: R128870672

Periodicals postage paid at Atlanta, GA. **POSTMASTER:** Send address changes to ***Emergency Medicine Reports***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $31. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Multiple copy prices: One to nine additional copies, $359 each; 10 to 20 additional copies, $319 each.

Accreditation

AHC Media LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media LLC designates this educational activity for a maximum of 60 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Approved by the American College of Emergency Physicians for 60 hours of ACEP Category 1 credit.

Emergency Medicine Reports has been reviewed and is acceptable for up to 39 Prescribed credits by the American Academy of Family Physicians. AAFP accreditation begins 01/01/07. Term of approval is for one year from this date. Each issue is approved for 1.50 Prescribed credits. Credit may be claimed for 1 year from the date of each issue. The AAFP invites comments on any activity that has been approved for AAFP CME credit. Please forward your comments on the quality of this activity to cmecomment@aafp.org.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman. Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Clinical, legal, tax, and other comments are offered for general guidance only; professional counsel should be sought for specific situations.

This CME activity is intended for emergency and family physicians. It is in effect for 24 months from the date of the publication.

AHC Media LLC

Subscriber Information

Customer Service: 1-800-688-2421

Customer Service E-Mail: customerservice@ahcmedia.com
Editorial E-Mail: shelly.mark@ahcmedia.com

World Wide Web page: http://www.ahcmedia.com

Subscription Prices

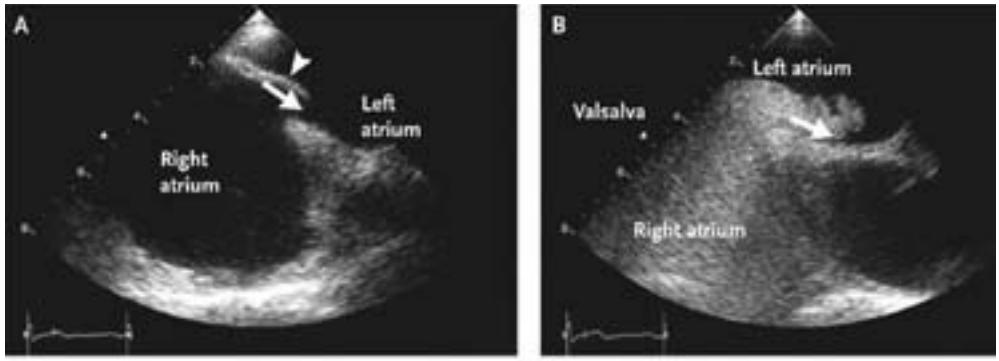
1 year *with* 60 ACEP/60 AMA/60 AAFP Category 1/Prescribed credits: $544
1 year *without* credit: $399
Add $12.95 for shipping & handling
Resident's rate $199
Discounts available for group subscriptions.
For pricing information, call Tria Kreutzer at (404) 262-5482.

All prices U.S. only.
U.S. possessions and Canada, add $30 plus applicable GST. Other international orders, add $30.

For Customer Service and CME questions,

Please call our customer service department at **(800) 688-2421.** For editorial questions or comments, please contact **Shelly Morrow Mark,** Specialty Editor, at shelly.mark@ahcmedia.com or (352) 351-2587.

Figure 1. Transesophageal Echocardiography of Patent Foramen Ovale (PFO)



A. TEE in longitudinal plane shows separation (arrow) between primum septum (arrowhead) and secundum septum. B. TEE with injection of agitated-saline contrast during Valsalva—there is passage of bubbles (arrow) through PFO into left atrium.
Used with permission from: Kizer D. Patent foramen ovale in young adults with unexplained stroke. *N Engl J Med* 2005;353:2361-2372. Copyright © 2005 Massachusetts Medical Society. All rights reserved.

to left shunt or a right to left shunt at rest, a diagnosis of pulmonary embolism, and the presence of an atrial septal aneurysm (ASA).[8] In fact, presence of both a PFO and ASA showed a 33-fold increase in cryptogenic stroke over the general population.[11] Patients with an ASA and PFO concurrently tend to have large PFOs, which may contribute to this increased risk.[12-14]

The diagnostic test of choice in patients with suspected PFO is transesophageal echocardiography (TEE). In one study, TEE was able to find the source of cardioembolism in 57% of patients with cryptogenic stroke as opposed to only 10-15% with transthoracic echocardiography.[15] Injection of agitated saline contrast into a peripheral vein can aid in the detection of a PFO via TEE by quantifying the number of bubbles that migrate from the right to the left atrium after three cardiac cycles.[16] (*See Figure 1.*)

The risk of recurrence of stroke in young patients who have a PFO is proportional to the size of the opening, the degree of shunting, and the presence of an ASA. However, the general rate of recurrence tends to be low in patients younger than the age of 60, ranging from 1.9% to 2.3%.[17,18]

Patients with a patent foramen ovale who have had a stroke have several therapeutic options, but the data comparing these options is limited. One treatment is anticoagulation with an antiplatelet agent, such as aspirin, clopidogrel, or dipyridomole. An alternative is treatment with warfarin. The data differentiating between aspirin, as opposed to warfarin, for anticoagulation is inconclusive but there was a slight increased risk of bleeding with warfarin.[18] Other options include direct surgical closure and percutaneous closure. It is unclear whether either of these closure techniques is superior to anticoagulation, but percutaneous closure is only FDA-approved for cases of recurrent stroke despite therapeutic oral anticoagulation.[19]

Cerebrovascular Dissection

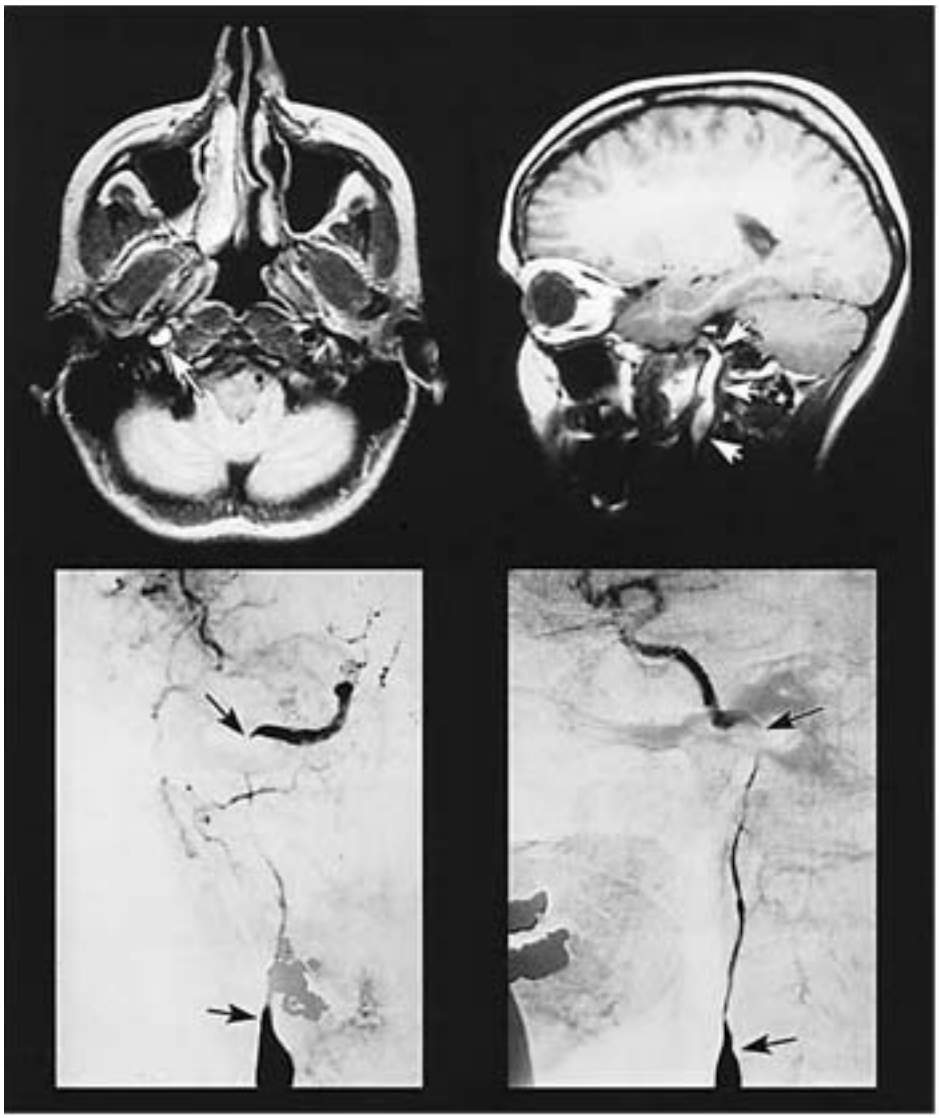
The annual incidence of spontaneous carotid artery dissection is 2.5-3 per 100,000, and the estimated frequency of vertebral artery dissection is 1-1.5 per 100,000. While dissection of the vertebral or carotid arteries accounts for only 2% of all ischemic strokes, they are an important cause of stroke in young people, and account for 10-25% of such cases.[20] Dissections of the cervical arteries affect all age groups, including the pediatric population, but there is a definite peak in the fifth decade. Men and women are affected equally, although women are on average five years younger at the time of dissection.

The pathophysiology of arterial dissection involves an intimal tear in the vessel, which allows blood to enter into layers of the arterial wall and form an intramural hematoma.[20] Such defects may follow significant trauma or occur spontaneously, although most dissections probably involve some minor trauma or mechanical stress to the artery.[21,22] Extracranial segments of the carotid and vertebral arteries experience dissection more often than intracranial segments or similar sized arteries elsewhere in the body. This increased prevalence in the arteries of the neck may be explained by the greater mobility of these extracranial segments and increased exposure to trauma. Once blood enters the arterial wall, the hematoma may extend either toward the intima or the adventitia. Subintimal dissection tends to cause stenosis of the vessel lumen, while subadventitial dissection may cause aneurismal dilation of the artery. The expanding intramural hematoma may cause arterial lumen compromise with hypoperfusion and ischemia, however the most common etiology of cerebral ischemia associated with dissection is the result of embolism of thrombotic material adherent to the narrowed lumen at the site of dissection.[23,24]

The pathogenesis of cerebral artery dissection is likely an interaction of genetic and environmental factors.[21] Most people experiencing an arterial dissection have an underlying structural defect of the artery wall, although the exact arteriopathy is impossible to define in most cases. Well described and inherited disorders associated with arterial dissection include Ehlers-Danlos syndrome, Marfan's syndrome, autosomal dominant polycystic kidney disease, as well as fibromuscular dysplasia and cystic medial necrosis. Genetic studies are on-going to further define inherited risk.[25]

Given a genetic predisposition, an inciting trauma or stress to the artery may cause cervical artery dissection. Direct blows to the neck, hyperextension, and even spinal manipulative therapy have been described as independent risk factors for dissection.[26,27] Spinal manipulative therapy may simply be coincidental, as patients seek manipulative therapy for neck and head pain, which may be the initial symptom of dissection. Certainly, it is prudent to consider cervical dissection in any patient with new or increased neck pain or the development of neurologic signs with-

Figure 2. MRI and Angiography of Dissection of Internal Carotid Artery



T_1-weighted MRIs, in axial and sagittal views, show intramural hematoma in right internal carotid artery (arrows). Carotid angiograms, in frontal and lateral views, show corresponding long segment of high-grade stenosis. Used with permission from: Schievink . Current concepts: Spontaneous dissection of the carotid and vertebral arteries. *N Engl J Med* 2001;344:898-906. Copyright © 2001 Massachusetts Medical Society. All rights reserved.

in days of manipulative therapy.[26] Finally, a recent case report raises the concern about arterial dissection and stroke after methamphetamine and cocaine use.[28]

The typical patient with a carotid artery dissection presents with pain on one side of the head, face, or neck accompanied by a partial Horner syndrome (oculosympathetic palsy) and followed by cerebral or retinal ischemia with hours or days. This classic triad of symptoms is found in fewer than one-third of patients,[20] but the presence of two of the three symptoms should strongly suggest the diagnosis. Pain is the most frequent manifestation of carotid dissection, occurring in 80%,[29] and is most often described as severe, constant, and throbbing. In a series where imaging of the cervical arteries was liberally applied, pain was the only symptom of cervical artery dissection in 8% of patients.[30] Oculosympathetic palsy, or a partial Horner syndrome, includes ipsilateral miosis and ptosis as sympathetic nerve fibers along the internal carotid artery are disrupted. Anhidrosis, the third component of a classic Horner syndrome, is not seen with dissection of the internal carotid, as facial sweating is innervated by sympathetic fibers from the external carotid artery. Other symptoms of the dissection itself may include pulsatile tinnitus (25%), a bruit audible to the patient because of proximity of the carotid to the ear and cranial nerve palsies (12%), especially of the hypoglossal nerve.[21] Intraluminal thrombotic material may subsequently embolize, causing transient ischemic attacks (TIAs) or cerebral infarcts (CVA), with symptoms including amaurosis fugax, hemiplegia, or dysphasia. Dissection of the internal carotid almost always causes deficits in the MCA distribution.[24]

Vertebral artery dissection typically presents with pain in the posterior neck or occipital head followed by ischemia in the posterior circulation. Neurologic symptoms may include pain or weakness in an arm as a result of cervical root involvement or brain stem infarcts, particularly of the lateral medulla leading to a Wallenberg's syndrome (including dysphagia, diplopia, Horner syndrome, vertigo, nausea, and vomiting).[31]

Diagnosis of cervical artery dissections requires first and foremost a high index of suspicion. Catheter angiography was the gold standard diagnostic test for many years. The most common finding on angiography is the so-called "string sign"—a long segment of narrowed lumen. Currently, MRA has essentially supplanted this invasive technique.[32] Intramural hematomas are shown as hyperdense signals on T1 weighted imaging and characteristically have a crescent shape adjacent to the lumen. (*See Figure 2.*) The need to rule out arterial dissection in the cervicocranial arteries is on a short list of indications for emergent MRI.[33] Increasingly, helical CT angiography is being recognized as an adequate diagnostic test, and thus the choice of diagnostic test is best made after discussion with local neurology and radiology to define the most appropriate, available test.

Because the cerebral ischemia associated with dissection of the carotid or vertebral artery is caused by embolization in the vast majority of cases,[21] antiplatelet therapy or anticoagulation is, in fact, the treatment of choice. Standard treatment of arterial dissection includes heparinization until adequate anticoagulation

with warfarin is accomplished, and maintaining an INR of 2.5-3.0 for 3-6 months.[34] Contraindications to anticoagulation include the presence of a large infarct with mass effect, hemorrhagic transformation of the infarct, and intracranial extension of the dissection, in which case antiplatelet therapy with aspirin (325 mg a day) is recommended. Anticoagulation or antiplatelet therapy is continued until a followup MRA at 3 or 6 months reveals healing of the intraluminal abnormalities.[34]

It is also possible to safely treat strokes secondary to arterial dissection with thrombolytics.[35,36] Local complications from extension of the intramural hematoma do not occur. Given current urgency to administer thrombolytic to acute stroke syndromes, particularly in younger patients with appropriate presentations and a negative head CT, these reports of the safety of thrombolysis in dissection are reassuring.

Generally, the prognosis of cervicocerebral artery dissection is quite good. The death rate from dissection of the carotid and vertebral arteries is less than 5%. Almost 70% of patients make a good recovery with no or little neurologic deficit. The risk of recurrent dissection in an unaffected artery is about 2% during the first month but then decreases to about 1% per year.[20]

Cerebral Venous Thrombosis

The spectrum of presentations for cerebral venous thrombosis (CVT) is diverse and can range from an isolated headache to altered mental status with focal neurological deficits. The wide, and sometimes subtle, range of presentations of CVT can lead not only to a missed diagnosis but also to a failure to diagnose a venous thrombus as the underlying cause of what appears to be a stroke in a young adult. Therefore, it is important as emergency medicine practitioners to understand the possible presentations of cerebral venous thrombosis as well as the causes and risk factors associated with this diagnosis.

Cerebral venous thrombosis is an entity that tends to affect young and middle-aged adults, with some predominance toward females. The underlying cause of CVTs can sometimes be traced to an underlying coagulopathy. Hypercoagulability factors such as factor V Leiden, antithrombin III deficiency, and protein C or protein S deficiency have all been known to play a role in the development of venous thrombosis.[37]

Pregnancy has long been described as an inciting factor for cerebral venous thrombosis with an increased incidence during the peripartum and postpartum period. The highest incidence seems to be in the postpartum period, and risk factors include hypertension in pregnancy and cesarean delivery.[38,39] The prognosis of peripartum CVT, however, tends to be better than that of CVT associated with other causes.[40]

The use of oral contraceptive pills (OCP) increases the risk of both venous and arterial thrombus in certain patients, and an increased risk of cerebral venous thrombosis is no exception.[41,42] The use of OCPs as the precipitant for cerebral venous thrombosis is more common in developed countries and also in women who have a concomitant coagulopathy or history of thrombosis.

Septic thromboses account for up to 10% of cerebral venous thrombosis and are a common cause of cavernous sinus thrombosis.[42] They are a well described complication of bacterial sinusitis and other face or neck infections. As opposed to inflammatory and coagulative causes, the onset of septic thrombosis tends to be more acute and carry a worse prognosis.[38]

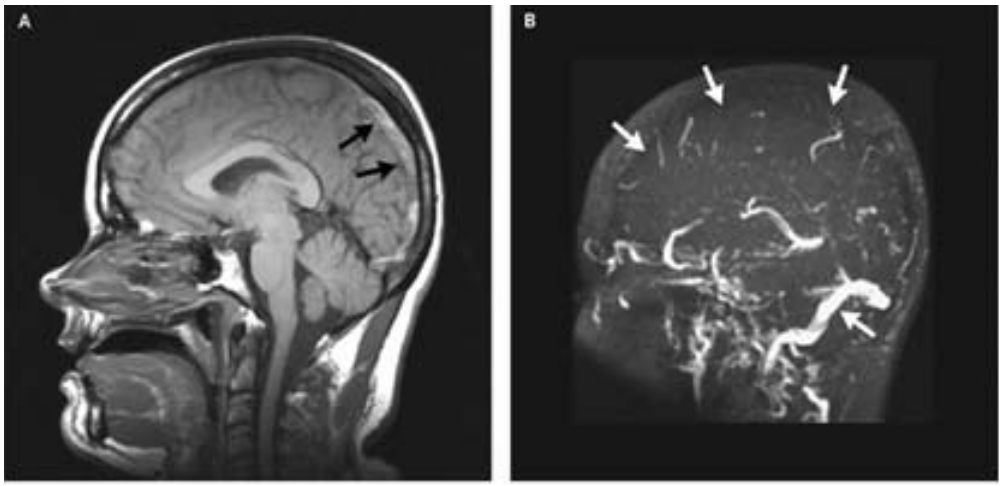
Table 2. Presenting Symptoms of Cerebral Venous Thrombosis

Headache	80%
Papilledema	50%
Impaired mental status	50%
Seizures	40%
Focal sensory or motor deficits	30-40%
Aphasia	
Hemianopia	
Cognitive disturbance	
Psychiatric disturbance	
Cranial nerve palsy	
Cerebellar signs	

Many factors affect the clinical presentation of cerebral venous thrombosis including patient age, the location and extent of the thrombus, and the rate of propagation of the thrombus. Headache is present in 80-95% of patients.[38] The headache tends to be severe, progressive, and persistent, but there is no classic manifestation of the headache and it can also present suddenly with either diffuse or localized pain.[43] About half of the patients with a diagnosis of CVT have an altered mental status, while 15% are comatose. Seizures, both partial and generalized, are common and found in more than 40% of patients. Focal neurological deficits, both motor and sensory, occur in 30-40% of patients. The unusual finding of focal deficits alternating from one side to another actually can be a late indication of a superior sagittal sinus thrombus. Another common finding is papilledema secondary to increased intracranial pressure, found in up to 50%.[44] (*See Table 2.*)

Depending on the site and acuity of the thrombus, these many symptoms generally coalesce into one of four clinical patterns.[38] Focal neurological deficits and/or parietal seizure predominate in the first of these patterns. This pattern is the one that is most likely to mimic the presentation of an acute ischemic stroke. In addition to motor or sensory deficits in the extremities, these patients may also have a headache and altered mental status. One exception is the rare incidence in which the cortical veins are involved but thrombus does not extend into the dural sinus. These patients have no signs of increased intracranial pressure, and their symptoms are very similar to an ischemic stroke. The second presentation, that of isolated increased intracranial pressure, can be mistaken for idiopathic intracranial hypertension and presents with headache, nausea, vomiting, and papilledema. This presentation may be more chronic, and late signs may include transient visual losses and eventually sixth nerve palsy.[38] A venous thrombus may also present itself as subacute diffuse encephalopathy. These patients tend to have no definitive localizing signs but have a decreased level of consciousness and occasionally seizures. They present similarly to a patient with encephalitis or a systemic

Figure 3. MRI of Sinus Thrombosis



A. T_1-weighted MRI in sagittal view reveals hyperintense signal in thrombosed superior sagittal sinus (arrows). B. MR venogram reveals absence of signal in superior sagittal sinus (upper arrows) and normal flow in transverse sinus (lower arrow). Used with permission from: Stam . *N Engl J Med* 2005;352:1795.

metabolic disturbance. The last pattern, painful ophthalmoplegia or cavernous sinus syndrome, is more distinct. This presentation is a constellation of symptoms that usually results from a septic thrombus. The thrombus originates either from direct extension from sinusitis or from hematogenous spread of a face or neck infection. These patients have proptosis, chemosis, painful extraocular movements, papilledema, and deficits of the third, fourth, or sixth cranial nerves.[41]

Although computed tomography (CT) is the most readily available and utilized imaging modality for acute intracranial processes in the emergency department, it is unfortunately not the study of choice for diagnosis cerebral venous thrombosis. Some patients may have positive CT findings such as the "empty delta sign" in which a superior sagittal sinus clot is outlined by contrast filling of collateral veins or the "dense triangle sign" in which a new clot in the superior sagittal sinus is actually visualized on a noncontrast CT. However, despite the presence of these signs and other nonspecific findings of hypodensities and blood from a secondary hemorrhage, 30% of patients will have a normal head CT.[38,45]

Magnetic resonance imaging (MRI) is the study of choice for the diagnosis of CVT.[38,42,45] MRI has the benefit of being able to visualize the clot directly but can be limited in the very early stages of the thrombus. In these cases, magnetic resonance venography (MRV) is particularly useful, with accuracy for diagnosing venous thrombosis approaching 100%.[43] (*See Figure 3.*) It has replaced conventional angiography in many institutions because of its availability and noninvasiveness. Helical CT venography is also becoming more readily available. CT venography has less artifact and generally can be obtained more quickly than MRV. In comparison to MRV, CT venography has been shown to have an accuracy of 90-100%.[46-48]

In some cases a lumbar puncture may be performed in these patients to rule out other potentially dangerous causes of headache such as subarachnoid hemorrhage and meningitis. While cerebrospinal fluid analysis is non-diagnostic for CVT, 50% have increased protein, 60% have increased RBCs, and 30% have leukocytosis.[44]

Heparin is the treatment of choice in patients diagnosed with cerebral venous thrombosis. It has been studied extensively and has been shown to be a safe and effective treatment, even in those patients with a secondary hemorrhagic infarct.[45,49,50] As with other types of venous thrombosis, heparin therapy eventually can be switched to oral warfarin. If the patient has no underlying coagulopathy, warfarin treatment should continue for 6 months to maintain an INR between 2.0-3.0.[45]

There has been discussion in the literature on the use of endovascular thrombolytics in these patients. However, although venous flow may be restored more quickly with the use of thrombolytics, there has been no evidence that there is any improvement in clinical outcome. There is an increased risk of hemorrhagic complications associated with thrombolytics when compared to heparin.[45] Considering the limited data regarding thrombolytics in this setting, their use should be restricted, but may be indicated in those cases in which there is decompensation despite therapeutic anticoagulation.

Several treatment options exist for those patients who have increased intracranial pressure (ICP) associated with CVT and they do not differ drastically from the treatment of increased ICP from other causes. In some cases, treatment of the thrombus with heparin alone will aid in the lowering of the intracranial pressure. Other patients with severe intracranial hypertension may require additional treatment with acetazolamide, mannitol, or glycerol. The role of corticosteroids in this setting is controversial and data is limited regarding their benefit.[38] Patients with vision-threatening papilledema may need one or more lumbar punctures to drain cerebrospinal fluid and decrease intracranial pressure.[51] In patients with refractory papilledema, optic nerve fenestration may be indicated. Ventriculoperitoneal shunts and, in rare cases, decompressive craniotomy may be necessary for severely increased intracranial pressure.

Although seizures are not uncommon, the use of seizure medications is not indicated prophylactically for all patients. Anticonvulsants should be started in patents who have already had a seizure or in those with a cerebral lesion on CT or MRI.[45]

Coagulopathies

In young patients who present with an ischemic stroke or cerebral venous thrombus and no clear identifiable cause, an investigation into underlying coagulopathies is sometimes war-

ranted. The yield of coagulopathic testing for all stroke patients is low; however the yield significantly increases when patients younger than the age of 50 years are selected for testing.[52,53]

Because the coagulopathies associated with venous thrombosis differ from those associated with arterial thrombosis, it is important to distinguish between patients with a venous thrombus as a source of their deficit, such as cerebral venous thrombosis or a paradoxical embolism, versus those presenting with an ischemic stroke originating from an arterial thromboembolism.[54] In patients with venous thromboembolism, factor V Leiden, as well as protein C deficiency, are the most commonly encountered underlying coagulopathies.[54] This differs from patients diagnosed with an ischemic stroke secondary to an arterial thrombus. The commonly diagnosed coagulopathies associated with ischemic strokes are antiphospholipid antibodies (also referred to as lupus anticoagulant or anticardiolipin antibodies), heparin antibodies, and elevated homocysteine level.[52,55] Other coagulopathies that patients may be screened for include antithrombin III deficiency, protein S deficiency, plasminogen deficiency, and prothrombin gene mutations.[54]

It is important that patients who initially screen positive for a coagulopathy such as protein C or S deficiency, antithrombin III deficiency, or anticardiolipin antibodies receive appropriate follow-up. Not only do these patients require longer-term anticoagulation but they should also be re-tested 2-3 months after the thrombotic event as initial laboratory tests may be falsely abnormal during the acute phase of a thrombus.[55]

Oral Contraceptive Pills

With more than 10 million women in the United States and 78.5 million women worldwide using oral contraceptive pills (OCPs), they are an important stroke risk factor.[56] The use of OCPs not only increases the risk of venous thromboembolism, but also the risk of ischemic stroke. Traditional oral contraceptive pills are associated with nearly a 3 times increased risk.[56] Although this risk is decreased with the use of newer OCPs that contain one-third to one-fifth the amount of ethinyl estradiol, some studies argue an increased risk still exists.[56,57] Co-factors that further compound the risk of stroke or thromboembolism includes hypertension, smoking, age over 35, and migraine headaches.[56,57]

Pregnancy

Stroke is a long described and potentially devastating complication of pregnancy. It can manifest as cerebral infarction, either venous or arterial, or as an intracranial hemorrhage.[58,59] The incidence of stroke during pregnancy still remains relatively rare, affecting about 24 of every 100,000 deliveries and the mortality rate, 4.1-14%, is lower than that of strokes in general.[60] Nonetheless, these events can still be debilitating. In one retrospective analysis, 14-22% of these patients were disabled enough to be discharged to another facility rather than home.[60] Factors that increased the risk of stroke during pregnancy or postpartum include hypertension, preeclampsia, concurrent infection, cesarean section, African-American race, and age greater than 35.[58,60] The time period in which the risk of pregnancy-related stroke is the greatest is not actually during pregnancy but during the six weeks postpartum.[61]

Spontaneous Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH) accounts for 10-15% of all cases of stroke, and is associated with the highest mortality rate, with only 38% of patients surviving one year.[62] While ICH is not more prevalent in a general younger population, there are several considerations that recommend that this diagnosis be included in a discussion of stroke in young people, including risk factor assessment and the extent of diagnostic evaluation.

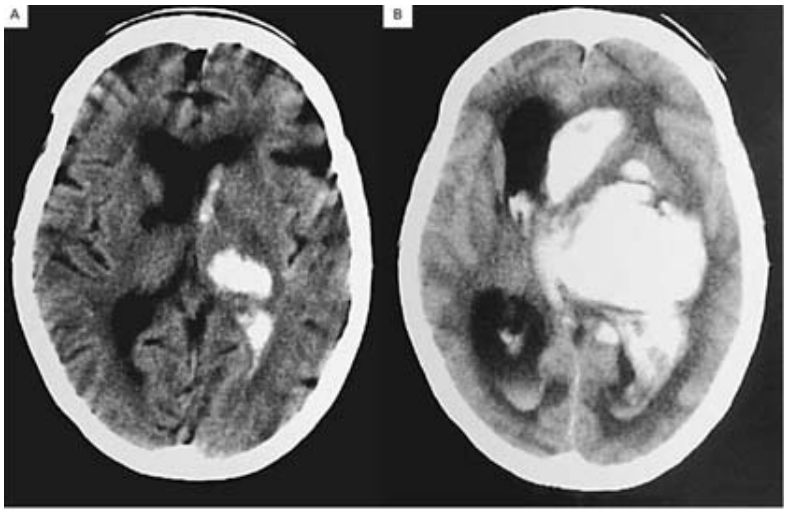
Primary intracerebral hemorrhage, which accounts for more than 80% of cases, occurs as a result of spontaneous rupture of small vessels damaged by chronic hypertension. Hypertension increases the risk of intracerebral hemorrhage, particularly in patients who are not compliant with medications, are 55 years of age or younger, or are smokers.[63,64] Improved control of blood pressure improves the incidence of hemorrhage, as does smoking cessation. Modifications of these risk factors are especially relevant in several genetic populations, including blacks and Japanese, who have a significantly increased risk of intracerebral hemorrhage (50-55 per 100,000 population, compared with 10-20 per 100,000 for overall worldwide incidence). Other important risk factors for intracerebral hemorrhage include alcohol and drug abuse, which are also pertinent to a younger population. Amphetamine abuse is associated with an increased risk of intracerebral hemorrhage, while cocaine use appears to increase the incidence of both hemorrhagic and ischemic strokes.[65]

Phenylpropanolamine, a synthetic sympathomimetic amine, gained notoriety in 2000 following a study that suggested that its inclusion in appetite suppressants, and possibly in cough and cold remedies, was an independent risk factor for hemorrhagic stroke in young women.[66] To put the risk into perspective, this article estimates that one woman may have a stroke due to this drug for every 107,000-3,268,000 women who use products with phenylpropanolamine as an appetite suppressant within a three-day window. In light of this study, phenylpropanolamine-containing products were removed from drugstore shelves.

There is an increasing incidence of anticoagulant-associated intracerebral hemorrhage. A recent study found the incidence has quintupled during the 1990s,[67] largely due to increasing use of warfarin for prevention of strokes associated with atrial fibrillation. The current incidence of anticoagulant-associated ICH approaches that of subarachnoid hemorrhage (6.6 cases per 100,000 persons), and accounts for 8-14% of all intracerebral hemorrhages.[68] Intracerebral hemorrhage with anticoagulation is also associated with a poor prognosis. The outcome is fatal in two-thirds of these patients with INR greater than 3.0 at presentation.

A final risk factor for intracerebral hemorrhage that is pertinent to a young population is the increased risk during pregnancy and postpartum (6.1 pregnancy-related ICH per 100,000 deliveries).[69] Intracerebral hemorrhage accounts for a substantial portion of pregnancy-related mortality. The risk of ICH associated with pregnancy is greatest in the postpartum period, and independent risk factors include advanced maternal age, African American

Figure 4. Rapid Expansion of Intracerebral Hemorrhage



A. The first CT was obtained one hour after presentation. B. The second CT was obtained six hours after presentation, following neurologic deterioration. Used with permission from: Qureshi, et al. Medical progress: Spontaneous intracerebral hemorrhage. *N Engl J Med* 2001;344:1454.

race, hypertensive disease, coagulopathy, and tobacco abuse.

Patients with intracerebral hemorrhage typically present with the abrupt onset of severe headache and developing neurologic deficits, or with decreased level of consciousness. Patients with a supratentorial intracerebral hemorrhage involving putamen, caudate, and thalamus have contralateral sensory-motor deficits due to involvement of the internal capsule. Patients with infratentorial bleeds will have signs of brain stem dysfunction, such as abnormalities of gaze, cranial nerve abnormalities, and contralateral motor deficits. Patients with hemorrhage within the cerebellum develop ataxia, nystagmus, and dysmetria. Nonspecific symptoms typically include headache and vomiting due to increased intracranial pressure and meningismus when blood extends to the ventricles. One-fourth of patients with intracerebral hemorrhage who initially are alert will have deterioration in level of consciousness within the first 24 hours after the onset of bleeding, usually associated with continued or recurrent bleeding. (*See Figure 4.*)

Intracerebral hemorrhage is diagnosed easily and reliably by non-contrast CT scan of the head. The location and size of the hematoma, the presence of interventricular blood, and the occurrence of hydrocephalus should be noted. Selected patients may need to undergo angiography (catheter angiography, or contrast enhanced MRI or helical CT) to look for secondary causes of hemorrhage, including aneurysms, arteriovenous malformations, and vasculitis. Nearly half of patients who are normotensive and 45 years of age or younger had abnormalities by angiography, whereas hypertensive patients older than 45 years rarely had a secondary cause of the bleed. The American Heart Association guidelines recommend angiography for all patients with no clear cause of hemorrhage who are candidates for surgery, particularly young patients without hypertension who are clinically stable.[70]

The medical management of intracerebral hemorrhage in the emergency department initially includes evaluation of the airway and decisions about intubation. This becomes a critical action for patients with decreased level of consciousness or impairment of airway protective reflexes. Approximately 30% of supratentorial hemorrhage, and virtually all patients with a brain stem or cerebellar hemorrhage have altered level of consciousness and will require intubation.[62] While aggressive treatment of hypertension in the setting of an acute intracerebral hemorrhage remains controversial, most authors agree that in the hypertensive patient (MAP > 130 mmHg), it is reasonable to decrease MAP by 15% with labetalol or nicardipine infusion. Finally, correction of a coagulopathy is of paramount importance. For the patient who has been using warfarin, rapid correction with fresh frozen plasma (15 mL/kg body weight) and vitamin K (2-10 mg IV) is standard care.[71] Unfortunately, vitamin K takes 6-24 hours to normalize the INR. Fresh frozen plasma, in volume sufficient to reverse a severe coagulopathy (often 2-4 liters) can be a limiting factor in seriously ill patients. More recent trends in the treatment of warfarin-associated coagulopathy include the use of prothrombin complex concentrates (PCC – factor IX concentrate) and recombinant factor VIIa (rFVIIa).[72]

For the patient with a Glasgow Coma Scale (GCS) score of ≤ 8, or with neurologic deterioration, emergent treatment of increased intracranial pressure is appropriate, and urgent neurosurgical consult for placement of an intracranial pressure (ICP) monitor is indicated. Temporizing measures that will decrease ICP until further interventions are available include hyperventilation and the use of mannitol (0.25-1.0 g/kg body weight).[71] Hyperventilation to a PCO_2 of 25 to 30 mmHg is highly effective and will rapidly lower ICP, but its effects are short-lived. Mannitol will have peak effects in approximately 20-30 minutes and may have a duration of action of several hours.

Surgical treatment of intracerebral hemorrhage remains controversial, although it is possible to state a few truths and review the current standard of care.[70-73] While neurosurgical consultation is appropriate for any patient with ICH, the urgency with which it needs to be accomplished will vary. For the patient with hydrocephalus on CT or secondary neurologic deterioration due to intraventricular blood, an external ventricular drain is appropriate. Ventriculostomy also allows ICP monitoring, which will facilitate treatment of increased ICP. For the patient with a cerebellar hemorrhage > 3 cm or hemorrhage of any size with neurologic deterioration, surgical evacuation is indicated. Finally, any large accessible cortical hematoma or secondary neurologic deterioration in a young patient mandates consideration of a neurosurgical procedure.[71]

The prognosis of intracerebral hemorrhage is poor, with 23-58% mortality at six months. Several factors are predictive of higher mortality—a low initial GCS, a large volume hematoma, and the presence of blood in the ventricular system.

Miscellaneous Causes of Stroke in Young People

Other considerations with stroke in young people include associations with HIV infection, cancer, sickle cell disease and trait, illicit drug abuse, and migraines. Finally, this discussion includes conversion reactions, which must be considered in the presentation of many young people with otherwise unexpected neurologic deficits.

Acquired immunodeficiency syndrome (AIDS) is strongly associated with stroke,[74] with one study reporting an increased adjusted relative risk of 14% for ischemic stroke and 25% for intracerebral hemorrhage.[75] While some have postulated a primary angiitis of the CNS associated with HIV infection,[76] it is clear that many strokes in these patients are secondary to associated infectious and neoplastic processes associated with AIDS.

Strokes, including hemorrhage and infarction, are second only to metastases in frequency of CNS lesions in autopsy series of patients with cancer. A recent large retrospective review of cancer patients with cerebral infarction found causes of infarction evenly distributed between embolic and nonembolic,[77] and a suggestion that a hypercoagulable state was a leading risk of stroke in this population, as evidenced by nonbacterial thrombotic endocarditis and other cardioembolic sources. Also noted was a higher frequency of stroke in patients with lung and primary intracranial cancer. Once stroke occurred in a patient with cancer, regardless of etiology, the overall prognosis was poor, with median survival of only 4.5 months.[77]

Stroke is a devastating complication of sickle cell disease and occurs in approximately 11% of those with hemoglobin SS younger than the age of 20, and may be associated, with intracranial hemorrhage, especially in the adult population.[78] In response to chronic anemia and hypoxemia, cerebral blood flow is markedly increased in sickle cell disease, as evidenced by increased velocity in major cerebral arteries by transcranial Doppler ultrasonography. When acute conditions arise leading to diminished oxygen availability, the increased hypoxic stress leads to ischemia, typically in the parenchymal areas of the anterior and middle cerebral arteries and the border zones between their distal circulations. It has even been suggested that sickle cell trait is a potential risk factor for stroke in the African-American population.[79]

The relationship between migraine and stroke has been shown by epidemiologic studies, and most conclude that a history of migraine is an independent risk for ischemic stroke.[80,81] A migranous infarct in which the pathogenesis is directly due to migraine is diagnosed when the stroke occurs during a typical migraine with aura and when other causes have been excluded. While this etiology of stroke in young people continues to appear in lists of population studies, it is probably wise to limit the use of this diagnosis, at least until an extensive search for other causes has been exhausted.

Finally, conversion reaction can present with a very convincing constellation of neurologic symptoms, which may appear to be an acute stroke. Typically there is the sudden onset of a single symptom, often simulating some nonpainful neurologic disorder for which there is no pathophysiologic explanation. The neurologic symptoms are not under the patient's voluntary control, the symptoms are often associated with antecedent stress (and occasionally have some symbolic relationship to the precipitant), and they may be associated with secondary gains. Almost one-third of patients with conversion reaction have a history of previous psychiatric diagnosis. *La belle indifference* refers to an apparent lack of concern by the patient for their symptoms, and has long been regarded as typical of conversion symptoms, although a recent study finds that this clinical sign does not reliably discriminate between conversion disorder and organic disease.[82]

Summary

Finally, evaluating a young person with stroke symptoms necessarily requires a broader differential than a similar presentation in an older population. The workup should include unique elements of history, examination, and diagnostic testing to rapidly diagnose and treat stroke syndromes common in the younger population. The history must include family history of thrombotic or vascular processes, as well as the patient's past history of migraine, prior thrombotic events, or diseases associated with risk (i.e., systemic lupus erythematosis), and medications (i.e., oral contraceptives, warfarin) or illicit drug use. Further, the history of the current event should query whether pain in the head or neck was present, and the temporal course of the symptoms.

The diagnostic evaluation must include a good neurologic examination with emphasis on pupils, cranial nerves, cerebellar function, as well as extremity motor and sensory findings. A GCS is appropriate on all patients with any decrease in level of responsiveness as a way of following neurologic status over time.

Routine laboratory studies should be drawn, including coagulation studies, and an electrocardiogram and cardiac monitoring should occur (in part, to rule out atrial fibrillation as a source of emboli). Concern about an embolic source of stroke in a young person should lead to a transesophageal echocardiography to evaluate intracardiac clots, as well as right to left shunts, including the presence of a PFO. A noncontrast CT scan is the appropriate first imaging test, and will reliably exclude intracerebral hemorrhage. Unfortunately, CT is notoriously unhelpful in cervical artery dissection and cerebral venous thrombosis. When there is concern for these two diagnoses, MRI with arterial and with or without venous phase contrast is appropriate, or at least helical CT with contrast.

References

1. Kristensen B, Malm J, Carlberg B, et al. Epidemiology and etiology of ischemic stroke in young adults aged 18 to 44 years in northern Sweden. *Stroke* 1997;28:1702-1709.
2. Lee TH, Hsu WC, Chen CJ, et al. Etiology study of young ischemic stroke in Taiwan. *Stroke* 2002;33:1950-1955.
3. Leys D, Bandu L, Henon H, et al. Clinical outcome in 287 consecutive young adults (15–45 years) with ischemic stroke. *Neurology* 2002;59:26-33.
4. Jacobs BS, Doden-Albala B, Lin IF, et al. Stroke in the young in the northern Manhattan Stroke Study. *Stroke* 2002;33:2789-2793.
5. Bogousslavsky J, Pierre P. Ischemic stroke in patients under age 45. *Neurol Clin* 1992;10:113-124.
6. Hagan PT, Scholtz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc* 1984;59:17-2.

7. Overell JR, Bone I, Lees KR. Interarterial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology* 2000;55:1172-1179, 2000.
8. Wu LA, Malouf JF, Dearami MD, et al. Patent foramen ovale in cryptogenic stroke. *Arch Intern Med* 2000;164:950-956.
9. Meissner I, Whinsnant JP, Khandheria BK, et al. Prevalence of potential risk factors for stroke assessed by transesophageal echocardiography and carotid ultrasonography: the SPARC study: Stroke Prevention: Assessment of Risk in a community. *Mayo Clin Proc* 1999;74:862-869.
10. Loscalzo J. Paradoxical embolism: Clinical presentation, diagnostic strategies, and therapeutic options. *Am Heart J* 1986;112:141-145.
11. Cabanes L, Mas JL, Cohen A, et al. Atrial septal aneurysm and patent foramen ovale as risk factors for cryptogenic stroke in patients less than 55 years of age: A study using transesophageal echocardiography. *Stroke* 1993;24: 1865-1873.
12. Agmon Y, Khandheria BK, Meissner I, et al. Frequency of atrial septal aneurysms in patients with cerebral ischemic events. *Circulation* 1999;99: 1942-1944.
13. Hanley PC, Tajik AJ, Hynes JK, et al. Diagnosis and classification of atrial septal aneurism by two-dimensional echocardiography: report of 80 consecutive cases. *J Am Coll Cardiol* 1985;6:1370-1382.
14. Mugge A, Daniel WG, Angermann D, et al. Atrial septal aneurysm in adult patients: A multicenter study using transthoracic and transesophageal echocardiography. *Circulation* 1995;91:2785-2792.
15. Rahmatullah AF, Rahko PS, Stein JH. Transesophageal echocardiography for the evaluation and management of patients with cerebral ischemia. *Clin Cardiol* 1999;22:391-396.
16. Homma S, Sacco MD. Patent foramen ovale and stroke. *Circulation* 2005; 112:1063-1072.
17. Mas J-L, Arquizan C, Lamy C, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N Engl J Med* 2001;345:1740-1746.
18. Bogousslavsky J, Barazi S, Jeanrenaud X, et al. Stroke recurrence in patients with patent foramen ovale: the Lausanne Study. *Neurology* 1996;46: 1301-1305.
19. Kizer JR, Devereux RB. Patent foramen ovale in young adults with unexplained stroke. *N Engl J Med* 2005;355:2361-2372.
20. Schievink WI. Spontaneous dissection of the carotid and vertebral arteries. *N Engl J Med* 2001;344:898-906.
21. Thani B, Munshi SK, Dawson SL, et al. Carotid and vertebral artery dissection syndromes. *Postgrad Med* J 2005;81:383-388.
22. Caplan LR, Biousse V. Cervicocranial arterial dissections. *J Neuro-Ophthalmol* 2004;24:299-305.
23. Benninger DH, Georgiadis D, Kremer C, et al. Mechanism of ischemic infarct in spontaneous carotid dissection. *Stroke* 2004;35:482-485.
24. Lucas C, Moulin T, Deplanque D, et al. Stroke pattern of internal carotid artery dissection in 40 patients. *Stroke* 1998;29:2646-2648.
25. Rubinstein SM, Peerdeman SM, van Tulder MW, et al. A systematic review of the risk factors for cervical artery dissection. *Stroke* 2005;36:1575-1580.
26. Smith WS, Johnston SC, Skalabrin EJ, et al. Spinal manipulative therapy is an independent risk factor for vertebral artery dissection. *Neurology* 2003; 60:1424-1428.
27. Ernst E. Manipulation of the cervical spine: A systematic review of case reports of serious adverse events, 1995-2001. *MJA* 2002;176:376-380.
28. McIntosh A, Hungs M, Kostanian V, et al. Carotid artery dissection and middle cerebral artery stroke following methamphetamine use. *Neurology* 2006; 67:2259-2260.
29. Lee VH, Brown RD, Mandrekar JN, et al. Incidence and outcome of cervical artery dissection. *Neurology* 2006;67:1809-1812.
30. Arnold M, Cumurciuc R, Stapf C, et al. Pain as the only symptom of cervical artery dissection. *J Neurol Neurosurg Psychiatry* 2006;77:1021-1024.
31. Arnold M, Bousser MG, Fahrni G, et al. Vertebral artery dissection: presenting findings and predictors of outcome. *Stroke* 2006;37:2499-2503.
32. Phan T, Huston J, Bernstein MA, et al. Contrast-enhanced magnetic resonance angiography of the cervical vessels. *Stroke* 2001;32:2282-2286.
33. Quint DJ. Indications for emergent MRI of the central nervous system. *JAMA* 2000;283:853-855.
34. Schievink WI. The treatment of spontaneous carotid and vertebral artery dissections. *Curr Opin Cardiol* 2000;15:316-321.
35. Arnold M, Nedeltchev K, Sturzenegger M, et al. Thrombolysis in patients with acute stroke caused by cervical artery dissection. *Arch Neurol* 2002;59: 549-553.
36. Georgiadis D, Lanczik O, Schwab S, et al. IV thrombolysis in patients with acute stroke due to spontaneous carotid dissection. *Neurology* 2005;64: 1612-1614.
37. Dentali F, Crowther M, Ageno W. Thrombophilic abnormalities, oral contraceptives and risk of cerebral vein thrombosis: A meta-analysis. *Blood* 2006; 107:2766-2773.
38. Crassard I, Bousser M. Cerebral venous thrombosis. *J Neuro-Ophthalmol* 2004;24:156-163.
39. Lanska DJ, Kryscio RJ. Risk factors for peripartum and postpartum stroke and intracranial venous thrombosis. *Stroke* 2001;31:1274-1282.
40. Vandenbroucke JP, Rosing J, Bloemenkamp K, et al. Oral contraceptives and the risk of venous thrombosis. *N Engl J Med* 2001;344:1527-1535.
41. DiNubile MJ. Septic thrombosis of cavernous sinuses. *Arch Neurol* 1988;45: 567-572.
42. Cumuriciuc F, Crassard I, Sarov M, et al. Headache as the only neurological sign of cerebral venous thrombosis: A series of 17 cases. *J Neurol Neurosurg Psychiatry* 2005;76:1084-1087.
43. Stam J. Thrombosis of the cerebral veins and sinuses. *N Engl J Med* 2005; 352:1791-1798.
44. Ameri A, Bousser MG. Cerebral venous thrombosis. *Neurol Clin* 1992;10: 87-111.
45. Ehtisham A, Stern B. Cerebral venous thrombosis: A review. *Neurologist* 2006;12:32-38.
46. Smith R, Hourihan MD. Rational imaging: Investigating suspected cerebral venous thrombosis. *BMJ* 2007;334:794-795.
47. Wetzel SG, Kirsch E, Stock KW, et al. Cerebral veins: Comparative study of CT venography with intraarterial digital subtraction angiography. *Am J Neuroradiol* 1999;20:249-255.
48. Khandelwal N, Agarwa A, Kochhar R. Comparison of CT venography with MR venography in sinovenous thrombosis. *Am J Roentgen* 2006;187: 1737-1743.
49. De Bruijin SFTM, Stam J. Randomized, placebo-controlled trial of anticoagulant treatment with low-molecular-weight heparin for cerebral sinus thrombosis. *Stroke* 1999;30:484-488.
50. Einhaupl KM, Villringer A, Meister W, et al. Heparin treatment in sinus venous thrombosis. *Lancet* 1991;338:597-600.
51. Ferro JM, Canhao MD, Stam MD. Prognosis of cerebral vein and dural sinus thrombosis: Results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). *Stroke* 2004;35:664-670.

52. Bousser MG, Chiras J, Bories J. Cerebral venous thrombosis-a review of 38 cases. *Stroke* 1985;16;199-213.
53. Bushnell CD, Siddiqu A, Goldstein LB. Improving patient selection for coagulopathic testing in the setting of acute ischemic stroke. *Neurology* 2001;57:1333-1335.
54. Busnell CD, Goldstein lB. Diagnostic testing for coagulopathies in patents with ischemic stroke. *Stroke* 2000;31:3067-3078.
55. Kahn MJ. Hypercoagulability as a cause of stroke in adults. *South Med J* 2003;96:350-353.
56. Bushnell CD, Goldstein LB. Physician knowledge and practices in the evaluation of coagulopathies in stroke patients. *Stroke* 2002;33:948-953.
57. Gillum LA, Mamidipudi SK, Johnston SC. Ischemic stroke risk with oral contraceptives: A meta-analysis. *JAMA* 2000;284:72-78.
58. Chan WS, Ray J, Wai, EK, et al. Risk of stroke in women exposed to low-dose oral contraceptives. *Arch Intern Med* 2004;164:741-747.
59. Witlin AG, Mattar F, Sibai BM. Postpartum stroke: A twenty-year experience. *Am J Obstet Gynecol* 2000;183:1:83-88.
60. Kittner SJ, Stern BJ, Feeser BR, et al. Pregnancy and the risk of stroke. *N Eng J of Med* 1996;335:768-774.
61. James A H, Bushnell CD, Jamison MG. Incidence and risk factors for stroke in pregnancy and the puerperium. *Obstet Genecol* 2005;106:509-516.
62. Qureshi AI, Tuhrim S, Broderick JP, et al. Spontaneous intracerebral hemorrhage. *N Engl J Med* 2001;344:1450-1460.
63. Badjatia N, Rosand J. Intracerebral hemorrhage. *Neurologist* 2005;11: 311-324.
64. Ariesen MJ, Claus SP, Rinkel GJE, et al. Risk factors for intracerebral hemorrhage in the general population. *Stroke* 2003;34:2060-2066.
65. Westover AN, McBride S, Haley RW. Stroke in young adults who abuse amphetamines or cocaine. *Arch Gen Psychiatry* 2007;64:495-502.
66. Kernan WN, Viscoli CM, Brass LM, et al. Phenylpropanolamine and the risk of hemorrhagic stroke. *N Engl J Med* 2000;343:1826-1832.
67. Flaherty ML, Kissela B, Woo D, et al. The increasing incidence of anticoagulant-associated intracerebral hemorrhage. *Neurology* 2007;68:116-121.
68. Thompson KM, Gerlach SY, Jorn KS, et al. Advances in the care of patients with intracerebral hemorrhage. *Mayo Clin Proc* 2007;82:987-990.
69. Bateman BT, Schumacher HC, Bushnell CD, et al. Intracerebral hemorrhage in pregnancy. *Neurology* 2006;67:424-429.
70. Juvela S, Kase CS. Advances in intracerebral hemorrhage management. *Stroke* 2006;37:301-304.
71. Manno EM, Atkinson JLD, Fulgham JR, et al. Emerging medical and surgical management strategies in the evaluation and treatment of intracerebral hemorrhage. *Mayo Clin Proc* 2005;80:420-433.
72. Aguilar MI, Hart RG, Kase CS, et al. Treatment of Warfarin-associated intracerebral hemorrhage: Literature review and expert opinion. *Mayo Clin Proc* 2007;82:82-92.
73. Mendelow AD, Unterberg A. Surgical treatment of intracerebral hemorrhage. *Curr Opin Crit Care* 2007;13:169-174.
74. Qureshi AI, Janssen RS, Karon JM, et al. Human immunodeficiency virus infection and stroke in young people. *Arcg Neurol* 1997;54:1150-1153.
75. Cole JW, Pinto AN, Hebel JR, et al. Acquired immunodeficiency syndrome and the risk of stroke. *Stroke* 2004;35:51-56.
76. Nogueeras C, Sala M, Sasal M, et al. Recurrent stroke as a manifestation of primary angiitis of the central nervous system in a patient infected with human immunodeficiency virus. *Arch Neurol* 2002;59:468-473.
77. Cestari DM, Weine DM, Panageas KS, et al. Stroke in patients with cancer: incidence and etiology. *Neurology* 2004;62:2025-2030.
78. Wang WC. The pathophysiology, prevent, and treatment of stroke in sickle cell disease. *Curr Opin Hematol* 2007;14:191-197.
79. Golomb MR. Sickle cell trait is a risk factor for early stroke. *Arch Neurol* 2005;62:1778-1779.
80. Milhaud D, Bogousslavsky J, van Melle G, et al. Ischemic stroke and active migraine. *Neurology* 2001;57:1805-1811.
81. Diener HC, Kurth T, Dodick D. Patent foramen ovale, stroke, and cardiovascular disease in migraine. *Curr Opin Neurol* 2007;20:310-319.
82. Stone J, Smyth R, Carson A, et al. La belle indifference in conversion symptoms and hysteria: systematic review. *Brit J Psychiatry* 2006;188:204-209.

Physician CME Questions

121. With intracerebral hemorrhage, which of the following CT scan findings is associated with poor outcome?
    A. Superficial lobar hemorrhage
    B. Intraventricular extension of bleed
    C. Internal capsule hemorrhage
    D. Cerebellar hemorrhage

122. In a patient under the age of 45 years, what is the most common cause of stroke symptoms?
    A. Dissection of the vertebral artery
    B. Cerebral venous thrombosis
    C. Embolism from cardiac source
    D. Atherosclerotic vascular disease

123. Of the following, which is considered an absolute contraindication to anticoagulant therapy following diagnosis of cervical dissection?
    A. Dissection of more than one artery
    B. Intracranial extension of the dissection
    C. Cerebellar infarction associated with vertebral dissection
    D. History of gastrointestinal bleeding

124. Which patient with an acute intracerebral hemorrhage should be referred for angiographic study to rule out an underlying vascular abnormality?
    A. A 40-year-old man with no significant medical history
    B. A 75-year-old man with history of diabetes
    C. A 50-year-old woman with hypertension
    D. A 65-year-old man with hypertension

125. What is the most common symptom of an internal carotid dissection?
    A. Partial Horner syndrome
    B. Pulsatile tinnitus
    C. Ipsilateral neck or head pain
    D. Amaurosis fugax

126. Which of the following increases the risk of stroke during pregnancy?
    A. Caucasian race
    B. Age younger than 21 years
    C. Multiparous female
    D. Hypertension

127. A 32-year-old female presents with headache, altered mental status, and seizure. An MRI/MRV shows a thrombus in the superior sagittal sinus with a small area of secondary hemorrhagic infarct. Which of the following statements regarding heparin therapy is correct?
   A. Heparin therapy is indicated in this patient.
   B. Heparin therapy should be started after complete resolution of the hemorrhagic infarct.
   C. Heparin therapy should only be used in combination with endovascular thrombolytics.
   D. Aspirin is a reasonable alternative to heparin in this patient.

128. Which of the following statements regarding the treatment of symptoms of a cerebral venous thrombosis is correct?
   A. Repeated lumbar puncture to treat papilledema should be avoided because of an increased incidence of spinal headache.
   B. Mannitol may be necessary to treat increased intracranial pressure.
   C. Heparin may exacerbate symptoms of increased intracranial pressure.
   D. Anticonvulsants should be started prophylactically for all patients with cerebral venous thrombosis.

129. Which of the following statements regarding radiologic imaging for cerebral venous thrombosis is most accurate?
   A. Head CT will typically have nonspecific but abnormal findings.
   B. MRI is most sensitive in the very early stages of the thrombus.
   C. CT venography has an accuracy that approximates that of MR venography.
   D. The "empty delta sign" on CT is a classic finding with cavernous sinus thrombosis.

130. A healthy 33-year-old male is diagnosed with an ischemic stroke. He had no history of atherosclerotic or vascular disease. Which of the following statements is most likely true?
   A. If the patient has a normal BMI, transthoracic echocardiography is sufficient to rule out the presence of a patent foramen ovale.
   B. The diagnosis of a patent foramen ovale can be ruled out if a primary source of thrombus is not identified.
   C. The presence of an atrial septal aneurysm along with a patent foramen ovale increases the risk of stroke.
   D. All patients with a patent foramen ovale will have a right to left shunt at rest when agitated saline contrast is injected.

CME Answer Key

121. B
122. C
123. B
124. A
125. C
126. D
127. A
128. B
129. C
130. C

In Future Issues: **Thrombocytopenia**

Emergency Medicine Reports CME Objectives

To help physicians:

- quickly recognize or increase index of suspicion for specific conditions;
- understand the epidemiology, etiology, pathophysiology, and clinical features of the entity discussed;
- apply state-of-the-art diagnostic and therapeutic techniques (including the implications of pharmaceutical therapy discussed) to patients with the particular medical problems discussed;
- understand the differential diagnosis of the entity discussed;
- understand both likely and rare complications that may occur.

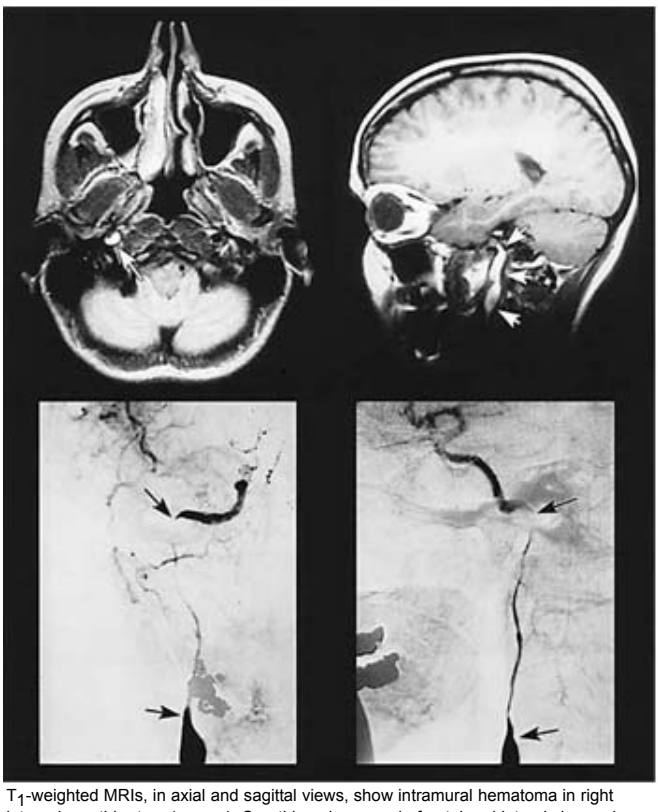
CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

Emergency Medicine Reports
The Practical Journal for Emergency Physicians

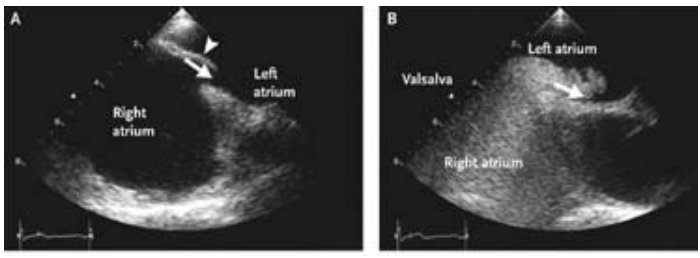
Stroke in Young People

MRI and Angiography of Dissection of Internal Carotid Artery



T_1-weighted MRIs, in axial and sagittal views, show intramural hematoma in right internal carotid artery (arrows). Carotid angiograms, in frontal and lateral views, show corresponding long segment of high-grade stenosis. Used with permission from: Schievink . Current concepts: Spontaneous dissection of the carotid and vertebral arteries. *N Engl J Med* 2001;344:898-906.

Transesophageal Echocardiography of Patent Foramen Ovale (PFO)



A. TEE in longitudinal plane shows separation (arrow) between primum septum (arrowhead) and secundum septum. B. TEE with injection of agitated-saline contrast during Valsalva—there is passage of bubbles (arrow) through PFO into left atrium.
Used with permission from: Kizer D. Patent foramen ovale in young adults with unexplained stroke. *N Engl J Med* 2005;353:2361-2372.

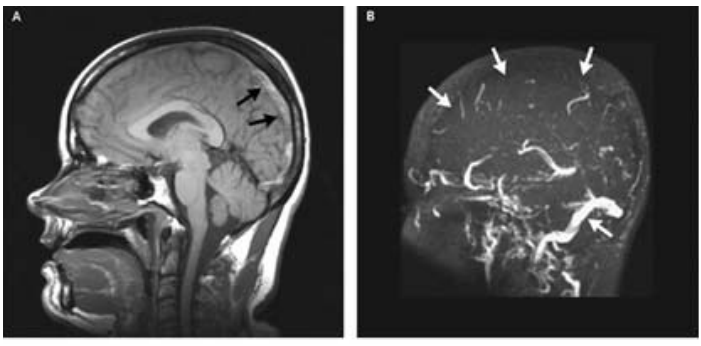
Presenting Symptoms of Cerebral Venous Thrombosis

Headache	80%
Papilledema	50%
Impaired mental status	50%
Seizures	40%
Focal sensory or motor deficits	30-40%
Aphasia	
Hemianopia	
Cognitive disturbance	
Psychiatric disturbance	
Cranial nerve palsy	
Cerebellar signs	

Causes and Incidence of Stroke in Young People

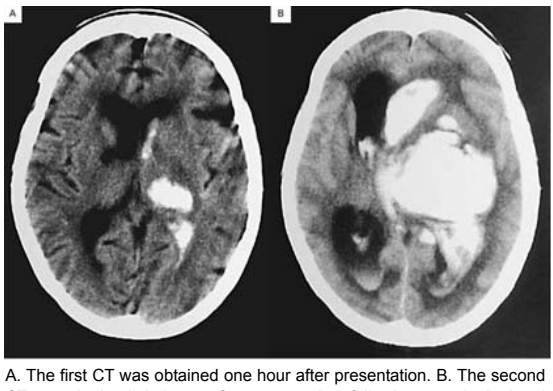
CAUSES OF STROKE IN YOUNG PEOPLE	%
Premature atherosclerotic disease	7–11
Cardioembolism, including PFO	6–33
Dissection of cervicocerebral arteries	8–20
Hematologic issues, including thrombophilia	7–10
Rare causes, including migraine, sickle cell, etc.	8–30
Unknown (cryptogenic)	21–60

MRI of Sinus Thrombosis



A. T_1-weighted MRI in sagittal view reveals hyperintense signal in thrombosed superior sagittal sinus (arrows). B. MR venogram reveals absence of signal in superior sagittal sinus (upper arrows) and normal flow in transverse sinus (lower arrow). Used with permission from: Stam . *N Engl J Med* 2005;352:1795. Copyright © 2005 Massachusetts Medical Society. All rights reserved.

Rapid Expansion of Intracerebral Hemorrhage



A. The first CT was obtained one hour after presentation. B. The second CT was obtained six hours after presentation, following neurologic deteric ration. Used with permission from: Qureshi, et al. Medical progress: Spontaneous intracerebral hemorrhage. *N Engl J Med* 2001;344:1454. Copyright © 2001 Massachusetts Medical Society. All rights reserved.

Supplement to *Emergency Medicine Reports*, December 10, 2007: "Stroke in Young People: A Different Differential." *Authors:* **Susan P. Torrey, MD, FACEP**, Associate Residency Director, Department of Emergency Medicine, Baystate Medical Center, Springfield, MA; and **Tala Elia, MD**, Attending Physician, Department of Emergency Medicine, Baystate Medical Center, Springfield, MA.
 Editors: Sandra M. Schneider, MD, FACEP, and J. Stephan Stapczynski, MD. **Senior Vice President and Group Publisher:** Brenda Mooney. **Associate Publisher:** Lee Landenberger. **Specialty Editor:** Shelly Morrow Mark. For customer service, call: **1-800-688-2421.** This is an educational publication designed to present scientific information and opinion to health care professionals. It does not provide advice regarding medical diagnosis or treatment for any individual case. Not intended for use by the layman.

Emergency Medicine Reports
The Practical Journal for Emergency Physicians

EMR121007TM

CME Evaluation

Please take a moment to answer the following questions to let us know your thoughts on the CME program. Fill in the appropriate space and return this page in the envelope provided. **You must return this evaluation to receive your certificate. ACEP members — Please see reverse side for option to mail in answers.** Thank you.

CORRECT ● INCORRECT ⊘ ✓ ✗ ⚠

1. If you are claiming physician credits, please indicate the appropriate credential: ○ MD ○ DO ○ Other _____

After participating in this program, I am able to:	**Strongly Disagree**	**Disagree**	**Slightly Disagree**	**Slightly Agree**	**Agree**	**Strongly Agree**
2. Recognize or increase index of suspicion for specific conditions.	○	○	○	○	○	○
3. Understand the epidemiology, etiology, pathophysiology, and clinical features of the entity discussed.	○	○	○	○	○	○
4. Apply state-of-the-art diagnostic and therapeutic techniques (including the implications of pharmacologic therapy discussed) to patients with the particular medical problems discussed.	○	○	○	○	○	○
5. Understand the differential diagnosis of the entity discussed.	○	○	○	○	○	○
6. Understand both likely and rare complications that may occur.	○	○	○	○	○	○
7. The test questions were clear and appropriate.	○	○	○	○	○	○
9. I am satisfied with customer service for the CME program.	○	○	○	○	○	○
10. I detected no commercial bias in this activity.	○	○	○	○	○	○
11. This activity reaffirmed my clinical practice.	○	○	○	○	○	○
12. This activity has changed my clinical practice.	○	○	○	○	○	○

If so, how? _____

13. How many minutes do you estimate it took you to complete this entire semester (13 issues) activity? Please include time for reading, reviewing, answering the questions, and comparing your answers with the correct ones listed. _____ minutes.

14. Do you have any general comments about the effectiveness of this CME program?

_____

I have completed the requirements for this activity.

Name (printed) _____ **Signature** _____

Please make label address corrections here or PRINT address information to receive a certificate.

PLEASE NOTE: If your correct name and address do not appear below, please complete the section at left.

Account # _____

Name: _____

Company: _____

Address: _____

City: _____ State: _____ Zip _____

Fax: _____ Phone: _____

E-mail: _____

In accordance with ACEP requirements, below we provide the option for ACEP members to submit their answers to this CME activity. If you wish to submit answers to this activity, please refer to Vol. 28, Nos. 14-26, and circle the correct responses.

CHRONIC PAIN: EVALUATION AND TREATMENT IN THE EMERGENCY DEPARTMENT

1. A B C D 2. A B C D 3. A B C D 4. A B C D 5. A B C D 6. A B C D 7. A B C D
8. A B C D 9. A B C D 10. A B C D

RIGHT LOWER QUADRANT PAIN IN FEMALES

11. A B C D E 12. A B 13. A B C D 14. A B 15. A B C D 16. A B C D 17. A B C D
18. A B C D E 19. A B C D 20. A B C D

ORTHOPEDIC PEARLS AND PITFALLS

21. A B C D 22. A B C D 23. A B C D 24. A B C D 25. A B C D 26. A B C D 27. A B C D
28. A B C D 29. A B C D 30. A B C D

FALLS ON THE OUT-STRETCHED HAND: PART I

31. A B C D 32. A B C D 33. A B C D 34. A B C D 35. A B C C 36. A B C D 37. A B C D
38. A B C D 39. A B C D 40. A B C D

FALLS ON THE OUT-STRETCHED HAND: PART II

41. A B C D 42. A B C D 43. A B C D 44. A B C D 45. A B C D 46. A B C D 47. A B C D
48. A B C D 49. A B C D 50. A B C D

CMS/JOINT COMMISSION HOSPITAL QUALITY MEASURES

51. A B C D 52. A B C D 53. A B C D 54. A B C D 55. A B C D 56. A B C D 57. A B C D
58. A B C D 59. A B C D 60. A B C D

EVALUATING AND TREATING ATRIAL FIBRILLATION IN THE EMERGENCY DEPARTMENT

61. A B C D 62. A B C D 63. A B C D 64. A B C D 65. A B C D 66. A B C D 67. A B C D
68. A B C D 69. A B C D 70. A B C D

ACUTE INFECTIOUS DIARRHEA

71. A B C D E 72. A B C D E 73. A B C D E 74. A B C D 75. A B C D 76. A B C D E 77. A B C D E
78. A B C D E 79. A B C D E 80. A B C D E

INFECTION CONTROL AND THE EMERGENCY DEPARTMENT

81. A B C D 82. A B C D 83. A B C D 84. A B C D 85. A B C D 86. A B C D 87. A B C D
88. A B C D 89. A B 90. A B C D

SEIZURES AND STATUS EPILEPTICUS IN ADULTS: PART I

91. A B C D 92. A B C D 93. A B C D 94. A B C D 95. A B C D 96. A B C D 97. A B C D
98. A B C D 99. A B C D 100. A B C D

SEIZURES AND STATUS EPILEPTICUS IN ADULTS: PART II

101. A B C D 102. A B C D 103. A B 104. A B C D 105. A B C D 106. A B C D 107. A B C D
108. A B C D 109. A B C D 110. A B C D

WITHDRAWAL OF TREATMENTS IN THE EMERGENCY DEPARTMENT

111. A B C D 112. A B C D 113. A B C D 114. A B C D 115. A B C D 116. A B C D 117. A B C D
118. A B C D 119. A B C D 120. A B C D

STROKES IN YOUNG PEOPLE

121. A B C D 122. A B C D 123. A B C D 124. A B C D 125. A B C D 126. A B C D 127. A B C D
128. A B C D 129. A B C D 130. A B C D

AHC Media LLC

Emergency Medicine Specialty Reports

Supplement S07181 **December 2007**

Physicians and Pharmaceutical Company Representatives

Authors: **John W. Hafner, MD, MPH, FACEP**, Assistant Clinical Professor of Surgery—Emergency Medicine, University of Illinois College of Medicine at Peoria, Department of Emergency Medicine, OSF Saint Francis Medical Center; and **Timothy Raines, MD**, Assistant, Department of Surgery, University of Illinois College of Medicine at Peoria, Department of Emergency Medicine, OSF Saint Francis Medical Center.

Peer Reviewer: **Jonathan Glauser, MD, FACEP**, Department of Emergency Medicine, Cleveland Clinic, Cleveland, OH.

It appears that it is going to be one of those days. Working a busy shift on a typical Monday, you have already diagnosed and treated patients with diffuse and nonspecific abdominal pain, chest pain, weakness/dizziness and resuscitated a full arrest—all before noon on the early a.m. shift. The charge nurse informs you that one of the loyal drug reps has stopped by the ED and brought a catered lunch for you and the staff in the back break room and would like a moment of your time. A clerk smiles and chimes in "be sure and pick up some pens and sticky pads for the front desk." Drawn by the prospect of a quick bite between patients on a relentless and demanding shift, you head back to the break room. The drug rep is a friendly, well-dressed and articulate professional, and at first seems mostly unconcerned about the product splashed all over the table in high gloss pamphlets. As you begin to help yourself to the food the drug rep introduces the new drug that appears to be an improved addition to the "standard" medications in its class. The rep discusses its improved palatability and dosing schedule, as well as a higher tissue concentration compared to its competitor. He seems to know how much you value evidence-based medicine and hands you a copy of an article detailing the drug's benefit in a recent clinical study. Impressed, you begin to take notice of the drug and look at the pamphlets in greater detail. The representative was also wondering if you like to play golf and "ever get away from the hospital" as he is sponsoring a small golf outing at a local country club for physicians that will include CME credits. Casually, he mentions that this drug is having some difficulty getting on the hospital's formulary, and that since the pharmaceutical and therapeutics committee is chaired by your emergency department director, you might be able to put in a good word for it.

Although this scenario may seem overreaching in its blatant pandering, it is actually a real life interaction that I experienced just prior to the enactment of the Pharmaceutical Research and Manufacturers of America (PhRMA) pharmaceutical representative physician interaction guidelines in 2002. Much has changed in the physician-pharmaceutical industry relationship since the enactment of stricter guidelines, but much has not. The pharmaceutical industry represents a legitimate facet of the American healthcare system, and much of the healthcare innovations we currently employ have been a result of private efforts. While it is important to recognize the accomplishments of the industry, it is also important for the physician to recognize the pitfalls. In this issue of Emergency Medicine Specialty Reports*, we will explore the pharmaceutical industry and its contact with the individual physician. Physician and industry perspectives as well as the government and other regulatory bodies will be discussed in order to bring national debates to the individual level.*

—The Editor

Statement of Financial Disclosure

To reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, Dr. Hafner (author and editor), Dr. Raines (author), and Dr. Glauser (peer reviewer) report no relationships with companies related to the field of study covered by this CME program.

Introduction

Many staff emergency physicians and resident physicians interact with pharmaceutical representatives on a regular basis. Usually the representatives bring information on their company's drugs as well as food that any hard-working, typically hungry emergency physician appreciates. The pens and other gifts representatives distribute may be appreciated, and they seemingly ask for nothing in return but a moment of the physician's time to speak about their product. It seems a fairly harmless interaction, with the emergency physician then returning to the daily grind in their busy emergency department. Many emergency physicians may feel that this contact is so brief that anything the representative says could not possibly affect their scope of practice in a meaningful way. Or does it? Emergency physicians should be asking themselves why pharmaceutical representatives, with the limited exposure to physicians during their busy ED shifts, continue to show up in their departments. One might envision financially savvy pharmaceutical companies losing money by paying highly trained employees to drive to various hospitals, coordinate a catered lunch for the physicians and staff, and deliver a limited presentation to an often disinterested audience. Why would arguably the most successful business industry in the world continue a marketing strategy that seems to be so ineffective? There has been much debate about how these visits and various other industry-related activities affect prescribing practices.

The relationship between physicians and the pharmaceutical industry can be viewed as a beneficial symbiosis of two components of the healthcare system bringing the latest innovations in treatments to patient care, or avaricious physicians willingly prescribing drugs from companies that offer them generous compensation for using their products. There has been increasing controversy regarding the relationship of physicians and pharmaceutical representatives for what exactly is considered an ethically acceptable or unacceptable interaction. The controversy stems from industry's contact with the holiest covenant in medicine—the physician-patient relationship. Sometimes the industry-physician interaction can result in a clear conflict of interest. A conflict of interest is a discrepancy between the personal interests and the professional responsibilities of a person in a position of trust.[1] This conflict of interest between the physician and industry can in some cases lead to detrimental effects on patient care, the medical profession in general, and violations of federal law. In fact, in some instances, the government has begun prosecuting pharmaceutical companies and physicians who violate these laws even though there was potential benefit to the individual patient. In 2004, after an extended investigation, Pfizer settled with the federal government for $430 million in fines and penalties for promoting its drug gabapentin (Neurontin) using lavish resort trips and hefty physician speaking and prescribing fees.[2] One year later Lincare agreed to a $10 million settlement with the federal government for allegedly bribing physicians with sporting event tickets, fishing trips, golf outings, gift certificates, and office and medical equipment.[2]

Other times the industry-physician interaction appears to be much more harmless and is often tied to legitimate sponsored medical education. These industry-physician exchanges are typically addressed by the medical governing bodies of particular specialties and an honor system is often employed that is founded on the assumption of the professionalism and beneficence of physicians for their patients. Unfortunately, not all physicians have adhered to the established guidelines, resulting in increasingly stringent criteria put forth by individual medical specialties in the face of potentially augmented federal regulations. Several physician-pharmaceutical company indiscretions earlier in this decade led to successful prosecutions that left both parties reeling and resulted in sweeping changes of the guidelines that were already in place. Many pharmaceutical companies themselves have even instituted an improved set of guidelines relating to their representatives' interactions with physicians, also in part due to the threat of increased federal regulation. At the center of the interaction is an often uneasy partnership: pharmaceutical companies using the effective marketing strategy of visiting physicians, promoting their products, and providing gifts to increase sales; and time- and resource-limited physicians attempting to treat their patients using the latest standard-of-care pharmaceutical products.

The Physician Perspective

Most physicians feel that they can interact with the pharmaceutical industry—even accept gifts—and still remain immune to specific influences. Physicians are intelligent scientific professionals who have been trained to make rational decisions about proper therapies for patients without being affected by a modest lunch or pen. One review found that most physicians deny that gifts could influence their behavior, and that most physicians are equivocal about the appropriateness of gifts from

Emergency Medicine Specialty Reports is published by AHC Media LLC, 3525 Piedmont Road, N.E., Six Piedmont Center, Suite 400, Atlanta, GA 30305. Telephone: (800) 688-2421 or (404) 262-7436.

Senior Vice President/Group Publisher: Brenda Mooney
Associate Publisher: Lee Landenberger
Specialty Editor: Shelly Morrow Mark
Marketing Manager: Shawn DeMario

GST Registration No.: R128870672

Periodical postage paid at Atlanta, GA. **POSTMASTER:** Send address changes to ***Emergency Medicine Specialty Reports***, P.O. Box 740059, Atlanta, GA 30374.

Accreditation

Emergency Medicine Specialty Reports' continuing education materials are sponsored and supervised by AHC Media LLC. Thomson American Health Consultants designates this continuing education activity for up to 1.5 hours in Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

AHC Media LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media LLC designates this educational activity for a maximum of 1.5 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman. Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Clinical, legal, tax, and other comments are offered for general guidance only; professional counsel should be sought for specific situations.

This CME activity is intended for emergency physicians. It is in effect for 24 months from the date of publication.

AHC Media LLC

Subscriber Information

Customer Service: 1-800-688-2421

Customer Service E-Mail: customerservice@ahcmedia.com
Editorial E-Mail: shelly.mark@ahcmedia.com
World Wide Web page: http://www.ahcmedia.com

For Customer Service and CME questions,

Please call our customer service department at **(800) 688-2421.** For editorial questions or comments, please contact **Shelly Morrow Mark,** Specialty Editor, at shelly.mark@ahcmedia.com or (352) 351-2587.

pharmaceutical representatives.[3] Physicians made distinctions about the ethical appropriateness that was reflected by the value of the gift, the type of gift, and the extent to which an activity conveys potential biased information.[3] Surveys reveal that physicians view small-value gifts as ethically more acceptable than larger valued gifts, and letters to medical journals assert the opinion that small gifts to physicians do not affect physician judgment toward a product.[4]

If physicians were able to maintain objectivity toward gifts, there would be no need for guidelines. Unfortunately it appears that physicians are not as objective as they believe themselves to be. Many physicians did not seem troubled by gifts and activities that are considered problematic by professional organizations such as the American Medical Association (AMA) and American College of Physicians (ACP).[3] One study documented a group of psychiatrists attending a grand rounds presentation whose speaker was sponsored by the manufacturer of quetiapine. Prior to the grand rounds presentation, two prescriptions were written for the drug, and 17 prescriptions were written afterward.[5] This study is consistent with other results showing that general practitioners who were visited more frequently by drug representatives were more likely to express views that led to unnecessary prescribing patterns.[6] Social science research has shown that even when individuals try to be objective during sales presentations, their judgment is subject to an unconscious and unintentional self-serving bias.[4]

While individual physicians often believe their judgment is immune from influence, they do not feel the same of their colleagues. A survey of medical students showed that significantly fewer students believed they would be influenced by gifts or food than believed that their colleagues would be influenced (31% vs. 42%, respectively).[7] A medical resident study was even more extreme, with 61% of respondents stating that promotions did not influence their practice, and only 16% believing the same about their colleagues.[8]

Different medical practices and residency programs deal with the issue of pharmaceutical representatives in different ways. Some utilize clear-cut guidelines, while others have limited or no guidelines. A study comparing two medicine residency programs in Canada, one restricting access to drug representatives and one allowing access, reveals that industry contact during training does create influence. Those residency program graduates who were visited by representatives with unrestricted access during training reported more pharmaceutical representative contact and an increased perceived benefit of the information provided.[9] The Board of the Council of Emergency Medicine Residency Directors (CORD) requested and approved a member survey regarding their beliefs and practices relating to industry sponsorship of speakers, social events, drug samples, travel to conferences, and the educational value of marketing representatives. Eight-five percent of EM program directors responded (106 CORD members) and the majority (72%) indicated never or rarely allowing unrestricted access to residents at work. Only 52% of directors never or rarely allowed representatives to give residents drug samples at work, and only 46% never or rarely allowed representatives to teach residents. In addition, two-thirds of program directors desired CORD guidelines regarding interaction with pharmaceutical industry.[10]

The Pharmaceutical Industry Perspective

Pharmaceutical companies are in a unique position of being a for-profit business providing products that assist in improving the length and quality of life. These companies spend on average more than $800 million to develop and test their products and bring them to market, including expenditures on failed projects and the value of forgone alternative investments.[11] Since these companies typically have only about 8-10 years of patent life on an innovative new drug before the drug becomes available as a generic, it is necessary to market the drug aggressively to recoup costs and generate income for future products. The medium through which pharmaceutical companies recuperate this income is the physician-based prescriptions. Collectively the pharmaceutical industry spends a substantial portion of its operating budget promoting its products, and the majority of this money is spent on pharmaceutical representative interactions with physicians. Sales force personnel account for the largest part of promotional spending, followed by direct-to-consumer advertising.[12] In 2000, there were 78,840 pharmaceutical representatives in the field, or one pharmaceutical representative for every 11 practicing physicians. Companies spent $431 million sending representatives to doctors' offices and $52 million more on hospital visits. The number of representatives nearly doubled between 1996 and 2000, selling pharmaceuticals to nearly 900,000 physicians in the United States.[13] In 2001, 84% of pharmaceutical marketing was directed toward physicians.[10]

There has been so much negative publicity directed toward the pharmaceutical industry and escalating prescription drug costs that the Congressional Budget Office performed a study in 2006 to evaluate pharmaceutical company spending and whether the prices of prescriptions were justified.[12] Some drug companies have sought to increase goodwill by subsidizing these medication costs and offering free drug samples that physicians can offer to patients. The pharmaceutical industry is also involved in offsetting the costs of continuing medical education (CME) conferences that at times might be difficult to produce or for some physicians to even attend. Since a number of these credits are required each year, the pharmaceutical industry is assisting in a component of education that is already mandatory.

Industry supported conferences, seminars, and symposia are helping physicians to provide the best, most appropriate, and most up-to-date health care to their patients.[14] The Accreditation Council for Continuing Medical Education (ACCME) showed in 1999 that industry support represented almost half of the $1.1 billion spent on CME.[14] It also states ACCME standards require that an accredited provider, such as a teaching institution, is responsible for the content, quality, and scientific integrity of all CME activities certified for credit.

Concerns for Interactions between Industry and Physicians

Some feel that even a limited role by a for-profit industry involved in the education of a scientific, objective, and beneficent field compromises the integrity of the physician-patient relationship. It has been noted that, with the approval of CME providers, pharmaceutical companies sometimes may prepare teaching slides and curriculum materials, and then compile lists of possible speakers and indirectly pay them.[15] This statement is concerning, as is the recent growth of the Medical Education and Communication Companies (MECC) industry. MECCs are for-profit companies that compile educational programs to be presented in hospital grand rounds and CME presentations, and provide teaching materials for physicians.[15] Many of these MECCs are accredited by the CME approving bodies, and can take full accountability for sponsoring their own CME programs. The problem becomes apparent when the support from these for-profit companies originates from the pharmaceutical industry.[15] This practice becomes suspicious and appears to be a way to skirt the ACCME policies in place to prevent product promotion.

As for the pharmaceutical representatives who visit hospitals and offices, studies have shown that they are not always forthcoming about their products in relation to other competing medications. It has been noted that 11% of statements made by multiple representatives speaking at 13 different presentations contradicted information readily available to them, and all inaccurate statement were favorable to the promoted drug.[16] There have been concerns with "preceptorships," in which a pharmaceutical representative spends a day shadowing the physician and seeing patients as "an educational experience," in which the physician receives an honorarium from the drug company in return.[17] This practice not only violates the patient-physician relationship, but also introduces a non-medical person into the room with the physician and patient, possibly violating privacy and HIPAA (Health Insurance Portability and Accountability Act) regulations. There is also increased concern from the federal government that gifts from the pharmaceutical industry could increase the cost of government healthcare programs such as Medicare and Medicaid.[18] In an effort to regulate costs, governments have been increasing their presence in issues relating to physicians and the pharmaceutical industry in this country and throughout the world. In the Netherlands, for example, acceptance of substantial hospitality from the pharmaceutical industry could result in criminal prosecution.[19]

Legal Implications

The year 2001 created a ripple effect that resulted in significant changes in the guidelines for how the pharmaceutical industry and physicians interact. The AMA, ACP, ACCME, as well as the pharmaceutical industry counterpart the Pharmaceutical Research and Manufacturers of America (PhRMA) overhauled their associated guidelines for one simple reason—to remain free from federal government regulation. In the past, these relationships have relied on the physician's conscience in these matters, but multiple concerns have brought this relationship to the attention of government officials. One of the key reasons is that the Medicare program has adopted a prescription drug benefit.[20] The government is interested in any conflicts of interest that may increase the expenditure for prescription medications. In addition the body of federal law dealing with "fraud and abuse" has expanded to the point where pharmaceutical companies and physicians involved in questionable marketing practices can now be prosecuted.

Anti-kickback legislation was instituted in 1972 that was created to protect Medicare and Medicaid from inappropriate expenditures and use of service.[20] It was initially used for clearly blatant industry violations, but since the early 1990s in situations where there is a partially lawful purpose in the relationship, a physician may still be prosecuted when there is also a clear unlawful purpose to the act.[20] Another law increasingly used by federal prosecutors is the False Claims Act that imposes civil liability on those who knowingly submit fraudulent claim or payment to the federal government.[21] Violations can result in fines from $5000 to $10,000 per claim plus three times the damages incurred by the government.[21]

The first major case where the anti-kickback and false claims laws were applied to physician and pharmaceutical company interactions was a class action lawsuit involving leuprolide acetate (Lupron). The federal government began investigating the marketing relationship of Takeda Chemical Industries and Abbott Laboratories (TAP) pharmaceuticals with various clinical urologists for the treatment of prostate cancer with the drug leuprolide. It was found the TAP encouraged urologists to bill Medicare at the average wholesale price for leuprolide, which the urologists received free or at discounted prices.[20] It was found that the company employed several physicians as "consultants" without requesting any specific or significant services in return. TAP was required to pay $290 million in criminal fines plus $585 million in civil penalties, addressing practices that had been delegated prior to this time as ethical oversight.[20] This successful prosecution led to other cases of similar pharmaceutical company practices, many of which were also successfully prosecuted. With the government setting its sights on regulating physician-pharmaceutical interactions, pharmaceutical and physician governing bodies revised their own guidelines to stem potential litigation.

Governing Bodies and Physician-Pharmaceutical Company Regulations

The ACGME created a set of guidelines to which CORD refers as their standard for interactions between physicians and pharmaceutical representatives released in 2002.[22] This set of guidelines, known as "The White Paper," was developed not only because of concern for individual physician relationships with the pharmaceutical industry, but also due to the learned behavior of residents observing the attendings' interaction with these representatives.[23] One of the six core competencies a resident must master during residency is professionalism, and this competency addresses the heart of the physician-pharmaceutical representative relationship. There are three principles that promote professionalism in programs and sponsoring institutions with regard to

Table 1. Principles Promoting Professionalism in Residency in Regard to the Pharmaceutical Industry

- Ethics and curricula must include instructions in and discussion of published guidelines regarding gift giving to physicians. These guidelines are found in "Gifts to Physicians from Industry" found in the Code of Medical Ethics of the American Medical Association, the Policy on Physician-Industry Relations of the American College of Physicians-American Society of Internal Medicine, and other medical specialties.
- Full and appropriate disclosure of sponsorship and financial interests is required at all program and institution-sponsored events, above and beyond those already governed by the Standards of Commercial Support promulgated by the ACCME.
- Programs and sponsoring institutions must determine through policy, which contacts, if any, between residents and industry representatives may be suitable, and exclude occasions in which involvement by industry representatives or promotion of industry products is inappropriate.[20]

relationships with the pharmaceutical industry. (*See Table 1.*)

The most updated AMA guidelines, revised in 2005, clarify what is ethically acceptable from the pharmaceutical industry in light of the increased policing of the physician-pharmaceutical relationship by the government. These guidelines now detail the specific kinds of gifts and honoraria that may be allowed, hoping to clarify some of the gray zones previously present. They even address funding for educational conferences sponsored by pharmaceutical companies and the selection process for residents who plan to attend them. (*See Table 2.*)

In emergency medicine, the American College of Emergency Physician's (ACEP) guidelines are simple, but somewhat vague. Regarding physician gifts, emergency physicians should only accept gifts of minimal value that benefit patients or serve an educational function only. They should also be willing to disclose all gifts received from biomedical companies. For educational conferences, ACEP's position is similar to the AMA guidelines, requiring participating physicians not to accept subsidies directly from pharmaceutical companies for conference, travel, or lodging. Faculty at conferences may accept fair compensation in regard to travel, lodging, and meals for time and service.[22] The Society of Academic Emergency Medicine (SAEM) has guidelines regarding commercial support of SAEM activities,[24] but no specific guidelines or policy regarding individual physician interactions with pharmaceutical companies.

The Department of Health and Human Services, Office of Inspector General, has developed a government policy aimed at reducing fraud and abuse in federal health care programs that was introduced in 2002. It explicitly states "this guide is not a compliance program. Rather it is a set of guidelines that pharmaceutical manufacturers should consider when developing and implementing a compliance program or evaluating an existing one."[25] The first element of the seven minimum recommended elements relates directly to physicians, stating that "the development and distribution of written standards of conduct, as well as written policies, procedures, and protocols that verbalize the company's commitment to compliance and address specific areas of potential fraud and abuse, such as … sales and marketing practices." To avoid increased federal regulation, the pharmaceutical industry quickly complied.

The pharmaceutical industry collectively developed a uniform set of guidelines addressing their representatives' interaction with physicians in 2002. The Pharmaceutical Research and Manufacturers of America (PhRMA) guideline highlights informal presentations by representatives. These presentations include modest meals as determined by local standards and occur in a venue and manner conducive to informational communication that provides scientific or educational value. Also addressed are professional meetings, where financial support will be given to the conferences' sponsors to offset the cost of those attending. When pharmaceutical companies underwrite conferences or meetings other than their own, responsibility for and control over the selection of content, faculty, educational methods, materials, and venue belongs to the organizers of the conferences or meetings in accordance with their guidelines. Pharmaceutical companies may provide financial support for meals to the CME conference provider as well as offer an additional reception in line with guidelines established by the conference provider, but time spent at these activities clearly must be subordinate to time spent at the educational activity. As far as practice and educational-related items, the cost of these items is not to exceed $100, and no items for personal use should be offered. It also states that no gift should be offered in a manner or on condition that would interfere with the independence of the physician's prescribing practices.[26]

The Compromise

Physicians' overarching and primary responsibility is to their individual patients, while the pharmaceutical industry's accountability is maintaining a reasonable profit for their shareholders. The pharmaceutical industry is at its core a business, and it cannot be expected to act on the patient's behalf as its primary motivation. This creates a conflict of interest for the physician. Conflicts of interests are "a set of conditions in which professional judgment concerning a primary interest (such as patient's welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain)."[27] Even the free drug samples that appear as beneficial gifts for patients often lead to physician prescribing pattern changes that ultimately profit the pharmaceutical companies. Research has shown that once a patient finishes a supply of free medication, the physician tends to write a prescription for the same brand, resulting in higher patient costs.[26] Although many new drugs today are "me-too drugs" (drugs in a similar pharmacologic class that have similar mechanisms of action but are made by a separate company), pharmaceutical companies are an important component of the healthcare industry because they develop drugs that advance medical care and assist physicians in better treating their patients.

Table 2. AMA Guidelines Regarding Physician-Pharmaceutical Interactions

- Any gift accepted by physicians individually should primarily entail a benefit to patients and should not be of substantial value. These include textbooks, modest meals, and other gifts if they serve a genuine educational function. Cash payment should not be accepted. The use of drug samples for personal or family use is acceptable as long as these practices do not interfere with patient access to drug samples. It would not be acceptable for non-retired physicians to request free pharmaceuticals for personal use or use by family members.
- Individual gifts of minimal value are permissible as long as the gifts are related to the physician's work (e.g., pens and notepads).
- The Council on Ethical and Judicial Affairs defines a legitimate "conference" as any activity, held at an appropriate location, where (a) the gathering is primarily dedicated to promoting objective scientific and educational activities and discourse (one or more educational presentation(s) should be the highlight of the gathering), and (b) the main incentive for bringing attendees together is to further their knowledge on the topic(s) presented. An appropriate disclosure of financial support should be made.
- Subsidies to underwrite the costs of continuing medical education conferences or professional meetings can contribute to the improvement of patient care and therefore are permissible. Since the giving of a subsidy directly to a physician by a company's representative may create a relationship that could influence the use of the company's products, any subsidy should be accepted by the conference's sponsor who in turn can use the money to reduce the conference's registration fee. Payments to defray the costs of a conference should not be accepted directly from the company by the physician.
- Subsidies from industry should not be accepted directly or indirectly to pay for the costs of travel, lodging, or other personal expenses of physicians attending conferences or meetings, nor should subsidies be accepted to compensate for the physicians' time. Subsidies for hospitality should not be accepted outside of modest meals or social events held as a part of a conference or meeting. It is appropriate for faculty at conferences or meetings to accept reasonable honoraria and to accept reimbursement for reasonable travel, lodging, and meal expenses. It is also appropriate for consultants who provide genuine services to receive reasonable compensation and to accept reimbursement for reasonable travel, lodging, and meal expenses. Token consulting or advisory arrangements cannot be used to justify the compensation of physicians for their time or their travel, lodging, and other out-of-pocket expenses.
- Scholarship or other special funds to permit medical students, residents, and fellows to attend carefully selected educational conferences may be permissible as long as the selection of students, residents, or fellows who will receive the funds is made by the academic or training institution. Carefully selected educational conferences are generally defined as the major educational, scientific, or policy-making meetings of national, regional, or specialty medical associations.
- No gifts should be accepted if there are strings attached. For example, physicians should not accept gifts if they are given in relation to the physician's prescribing practices. In addition, when companies underwrite medical conferences or lectures other than their own, responsibility for and control over the selection of content, faculty, educational methods, and materials should belong to the organizers of the conferences or lectures.[28,29]

On an individual physician level, research shows that basically any gift will bias a physician. The guidelines set in place by most of the professional organizations refer to inexpensive gifts for office use, low-cost educational or patient care gifts, and modest hospitality (reception with food and drink) that is connected with a legitimate educational program as acceptable. Those "acceptable gifts" can still lead to increased formulary expenses for hospitals. Two studies identified risk factors for increased requests for formulary additions of a drug (most of the formulary addition requests representing drugs felt to be of "little or no advantage" over existing formulary drugs): interaction with pharmaceutical representatives; receiving industry-sponsored meals, conference, or travel subsidy; accepting an industry-paid honorarium to speak at an event, and industry-sponsored research funding.[30] Similarly stated, there are 3 interactions with physicians that influence prescribing behavior: pharmaceutical representative speakers, CME sponsorship, and industry-sponsored conference travel.[31]

Some individual physicians or groups are involved in industry sponsored clinical trials. Physicians should not participate in studies that are, in effect, thinly disguised promotional schemes to entice physicians to use a new drug.[32] Another area of concern for physician bias and potential conflict of interest is physician investments in pharmaceutical and biomedical companies. This obviously can create a moral dilemma, and is an issue that has not been addressed by any of the major medical governing bodies based on the current recommendations available at this time.

In reference to residency training programs, many rely on pharmaceutical company financial support of CME programs and conferences. While guidelines became more specific in 2002, they are still not difficult to skirt.[33] Anyone presenting educational information to physicians-in-training for which segments were provided by industry should disclose this information, and faculty and program directors may accept honoraria or subsidies only for services rendered and reasonable travel expenses. It also has been shown that interaction with pharmaceutical representatives during residency does affect the perception of practicing physicians during their medical career, where those unexposed were half as likely to view educational information and sponsored activities as helpful. A recent systematic review revealed the majority of resident physicians reported insufficient training about how to interact with pharmaceutical representatives, and almost half desired more teaching on the subject.[34] In emergency medicine residency programs, residents were more likely than faculty to believe that

gifts were an appropriate way to learn about new products.[35]

In conclusion, physicians should be aware of the relative inability to remain objective in relationships with pharmaceutical representatives as well as what constitutes an acceptable gift. It is each individual physician and residency program's responsibility to monitor their own professionalism as defined by the ACGME White Paper and our collective responsibility to patients to be aware of compromised objectivity in relation to gifts from the pharmaceutical industry. Once physicians are aware of their weaknesses, then those weaknesses may more easily be addressed.

References

1. Orlowski JP. The hospital ethics committee and conflicts of interest in the health care environment. HEC Forum 1994;6:3-11.
2. Miller JB. Pharmaceutical company marketing practices. *Physician's News Digest* September, 2007.
3. Brett AS, Burr W, Moloo J. Are gifts from pharmaceutical companies ethically problematic?: a survey of physicians. *Arch Int Med* 2003; 163:2213-2218.
4. Dana J, Loewenstein G. A social science perspective on gifts to physicians from industry. *JAMA* 2003;290:252-255.
5. Dieperink ME, Drogemuller L. Industry-sponsored grand rounds and prescribing behavior. *JAMA* 2001;285:1443-1444.
6. Watkins C, Moore L, et al. Characteristics of general practitioners who frequently see drug industry representatives: national cross sectional study. *BMJ* 2003;326:1178-1179.
7. Sierles FS, Brodkey AC, et al. Medical student exposure to drug company interactions. *JAMA* 2005;294:1034-1042.
8. Steinman MA, Shlipak MG, McPhee SJ. Of principles and pens: attitudes of medicine housestaff toward pharmaceutical industry promotions. *Am J Med* 2001;110:551-557.
9. McCormick BB, Tomlinson G, Grill-Edwards P, Detsky A. Effect of restricting contact between pharmaceutical company representatives and internal medicine residents on posttraining attitudes and behavior. *JAMA* 2001;286:1994-1999.
10. Keim SM, Mays MZ, Grant D. Interaction between emergency medicine programs and the pharmaceutical industry. *Acad Emerg Med* 2004;11:19-26.
11. Marron DB. A CBO study: research and development in the pharmaceutical industry. Congressional Budget Office 10/2006; www.cbo.gov.
12. Sellers LJ, Brichacek A. Flexing their budgets: big pharma spending trends. *Pharmaceutical Exec* 2001; www.pharmexec.com.
13. Rasack J. Residency program addresses drug company influence. *Psychiatry News* 2001; 36:13 pg 5.
14. Holmer AF. Industry strongly supports continuing medical education. *JAMA* 2001;285:2012-2014.
15. Relman AS. Separating continuing medical education from pharmaceutical marketing. *JAMA* 2001;285:2009-2112.
16. Ziegler MG, Lew P, Singer BC. The accuracy of drug information from pharmaceutical sales representatives. *JAMA* 1995;273:1296-1298.
17. Wall LL, Brown D. Pharmaceutical sales representatives and the doctor/patient relationship. *Amer Col Obst Gyn* 2002;100:594-599.
18. Marwick C. Drug companies defend rewards to doctors for switching treatments. *BMJ* 2003; 326:67.
19. Sheldon T. GPs warned on accepting hospitality from drug companies. *BMJ* 2001;322:194.
20. Studdert DM, Mello MM, Brennan TA. Financial conflicts of interest in physicians' relationships with the pharmaceutical industry-self regulation in the shadow of federal prosecution. *N Engl J Med* 2004;351:1891-1900.
21. 31 U.S.C. (section)(section) 3729-3733 (2007).
22. ACEP. Gifts to physicians from biomedical industry. www.acep.org last updated 2005.
23. ACGME. Principles to guide the relationship between graduate medical education and industry (white paper). www.acgme.org 2002.
24. SAEM. Commercial support of SAEM activities. www.saem.org last updated 2007.
25. Department of Health and Human Services, Office of Inspector General. OIG compliance program guidance for pharmaceutical manufacturers. Federal Register 2003; vol 68 no 86:23731-23743.
26. Pharmaceutical Research and Manufacturers of America. Code on interactions with healthcare professionals. www.phrma.org last updated 2007.
27. Wazana A, Primeau F. Ethical considerations in the relationship between physicians and the pharmaceutical industry. *Psych Clin North Am* 2002;25, issue 3.
28. AMA. AMA (gifts to phys CME) ethical opinions and guidelines. www.ama-assn.org/ama/pub/category/print/4001.html last updated 2005.
29. AMA. Interactions with pharmaceutical industry representatives. www.ama-assn.org/ama/pub/category/11910.html last updated 2007.
30. Coyle SL. Physician-industry relations. Part 1: individual physicians. *Ann Int Med* 2002;136:396-402.
31. Wazana A. Physicians and the pharmaceutical industry: is a gift ever just a gift? *JAMA* 2000;283:373-380.
32. Backer EL, Lebsack JA, Van Tonder RJN, Crabtree BF. The value of pharmaceutical representative visits and medication samples in community-based family practices. *J Fam Prac* 2000;49:811-816.
33. Coyle SL. Physician-industry relations. Part 2: organizational issues. *Ann Int Med* 2002;136:403-406.
34. Zipkin DA, Steinman MA. Interactions between pharmaceutical representatives and doctors in training. *J Gen Intern Med* 2005;20:777-786.
35. Keim SM, Sanders AB, Witzke DB, et al. Beliefs and practices in emergency medicine faculty and residents regarding professional interactions with the biomedical industry. *Ann Emerg Med* 1993;22:1576-1581.

Physician CME Questions

1. Regarding pharmaceutical industry influence, most physicians:
   A. believe that their colleagues are free from influence.
   B. view small-value gifts as ethically more acceptable than larger value gifts.
   C. have almost no exposure to pharmaceutical representatives in

residence training.

D. feel that pharmaceutical gifts are highly influential in prescribing practices.

2. The pharmaceutical industry:
   A. spends approximately $8 million to develop and bring a drug to market.
   B. had one pharmaceutical representative for every 11 practicing physicians in the year 2000.
   C. sponsored about one-quarter of the $1.1 billion spent on physician CME in 1999.
   D. spent approximately $40 million on sending representatives to physicians' offices in the year 2000.

3. Which of the following would be considered an ethically appropriate gift to a physician from a pharmaceutical representative, according to the AMA guidelines?
   A. Golf balls
   B. Movie tickets
   C. Pens
   D. An honorarium for prescribing patterns

4. According to the AMA, all of the following statements concerning pharmaceutical industry sponsored CME are true *except*:
   A. Subsidies to underwrite the costs of continuing medical education conferences or professional meetings can contribute to the improvement of patient care and are therefore permissible.
   B. Subsidies for hospitality should not be accepted outside of modest meals or social events held as part of a conference or meeting.
   C. Physicians can be reimbursed for their time spent at a conference.
   D. Payments to defray the costs of a conference should not be accepted directly from the company by the physician.

5. According to the AMA, gifts from pharmaceutical representatives:
   A. should primarily entail a benefit to patients.
   B. should be of no substantial value.
   C. should *not* be accepted if there are strings attached.
   D. are acceptable in cash payments as long as they are less than $1000.

6. All of the following statements regarding Medical Education and Communication Companies (MECC) are true *except*:
   A. MECCs are for-profit companies that compile educational programs to be presented at grand rounds and CME presentations.
   B. Their presentations' content is always reviewed by independent CME approval bodies, limiting bias in the information compiled.
   C. They provide teaching materials for physicians.
   D. They may receive direct support by pharmaceutical companies.

CME Answer Key

1. B
2. B
3. C
4. C
5. D
6. B

Emergency Medicine Specialty Reports

CME Objectives

Upon completion of the article:

• the emergency medicine healthcare participant will be able to identify and describe key points in selected topics of medical ethics, infectious disease and HIV management, domestic violence, and pain management.

• for the presented topic, the learner will be able to describe the recent medical literature findings and relevant procedures useful in the clinical care of the emergency department patient.

• participants will understand the anatomic, physiologic, and clinical findings associated with emergency medicine disease and injury processes,

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that provided and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

In Future Issues: **Medication Error Prevention**

Emergency Medicine Specialty Reports

S07181TM

CME Evaluation

Please take a moment to answer the following questions to let us know your thoughts on the CME program. Fill in the appropriate space and **fax this page to 1-800-850-1232. You must return this evaluation to receive your certificate.** Thank you.

CORRECT ● **INCORRECT** ⊘ ✓ ✗ ⚠

1. If you are claiming physician credits, please indicate the appropriate credential: ○ MD ○ DO ○ Other _____

	Strongly Disagree	Disagree	Slightly Disagree	Slightly Agree	Agree	Strongly Agree
After participating in this program, I am able to:						
2. Identify and describe key points in selected topics of medical ethics, infectious disease and HIV management, domestic violence, and pain management.	○	○	○	○	○	○
3. Describe the recent medical literature findings and relevant procedures useful in the clinical care of the emergency department patient.	○	○	○	○	○	○
4. Understand the anatomic, physiologic, and clinical findings associated with emergency medicine disease and injury processes.	○	○	○	○	○	○
5. The test questions were clear and appropriate.	○	○	○	○	○	○
6. I am satisfied with customer service for the CME program.	○	○	○	○	○	○
7. I detected no commercial bias in this activity.	○	○	○	○	○	○
8. This activity reaffirmed my clinical practice.	○	○	○	○	○	○
9. This activity has changed my clinical practice.	○	○	○	○	○	○

If so, how? _____

10. How many minutes do you estimate it took you to complete this activity? Please include time for reading, reviewing, answering the questions, and comparing your answers with the correct ones listed. _____ minutes.

11. Do you have any general comments about the effectiveness of this CME program?

_____

I have completed the requirements for this activity.

Name (printed) _____ **Signature** _____

Please make label address corrections here or PRINT address information to receive a certificate.

PLEASE NOTE: If your correct name and address do not appear below, please complete the section at left.

Account # _____

Name: _____

Company: _____

Address: _____

City: _____ State: _____ Zip _____

Fax: _____ Phone: _____

E-mail: _____