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Common Misdiagnoses of Myocardial Infarction

Remember how you were told in medical school that history is 90% of diagnosis? Was it usually ascribed to William Osler or another such legendary figure? Do you still believe it? I don't, or at least as not as much as I once did. What's changed? Well, we know more. We have more diagnostic techniques that enable us to ferret out the atypical presentations of disease and expose the limitations of clinical diagnosis. Did Sir Osler have to deal with a diagnosis made by MRA in a patient with vague symptoms?

This issue continues the discussion of missed MIs, focusing on how to distinguish infarction from other causes of chest pain. A continual challenge, especially with lethal disorders such as aortic dissection and pulmonary embolism in the differential.

I will close with another quote from Sir Osler: "There is no disease more conducive to clinical humility than aneurysm of the aorta." I can't say it any better than that.

—J. Stephan Stapczynski, MD, Editor

One of the problems facing emergency physicians attempting to diagnose every acute myocardial infarction (MI) patient is that the complaint of chest pain is both very common and results from a wide variety of causes. Further, while many causes of chest pain are benign and self-limited (reflux, anxiety, musculoskeletal pain), some causes can be emergent and deadly if untreated (aortic dissection, pulmonary embolism). Several studies that specifically analyzed patients with missed MI in the ED have identified some common misdiagnoses.[1-4] For example, Pope, et al., listed the following discharge diagnoses for 19 patients with missed MI: 47% were diagnosed with non-cardiac chest pain, 16% with pulmonary problems, and 11% with stable angina.[1] Examples of non-cardiac diagnoses include "atypical" chest pain (32%), musculoskeletal pain (21%), and gastrointestinal pain (5%). These conditions will be discussed briefly to identify strategies that may help discover patients with acute MI before they are discharged with one of these diagnoses. In addition, dangerous diseases that can be confused with acute MI, such as aortic dissection and pulmonary embolism (PE), also will be discussed.

Dangerous Conditions Confused with Acute MI

These patients are not among the missed MIs sent home, but they represent the other side of the coin: those who are admitted with misdiagnosis of MI. While these misdiagnoses occur less often than patients discharged with MI, it is useful to review these conditions briefly in the context of misdiagnosis of MI.

Thoracic Aortic Dissection. Compared to acute MIs, acute thoracic aortic dissections are rare. There were 1.2 million acute MIs presenting to EDs in the United States in 2008,[5] but the average number of aortic dissections per year ranges from 2000–7000.[6,7] This means that, on average, an ED physician will see up to 600 MI patients for every 1 aortic dissection. Risk factors are similar for both conditions (hypertension, cigarette smoking), and in both situations older patients present with acute chest pain. One recent review of 90 aortic dissection patients found that 67% developed acute dissection during exertion or emotional events,[8] triggers traditionally associated more often with acute coronary syndrome (ACS) than with dissection. While most dissections occur in patients in their 60s

Executive Summary

- "Non-cardiac chest pain" is the most common ED discharge diagnosis seen in the missed-MI patient.
- Abrupt onset of pain is the most reliable symptom in patients with aortic dissection.
- The common problems of heartburn, chest wall tenderness, and anxiety can occur in patients with ischemic heart disease, thereby confusing the clinical picture.
- Patients are at low risk for MI or sudden death if they have had either a normal perfusion stress test within the past 2 years or a normal cardiac catheterization within the past 5 years.

and 70s, select younger patients also are at risk. Patients with bicuspid aortic valves, connective tissue disorders (Ehlers-Danlos), pregnant women, and crack cocaine users are at heightened risk.[7] Ehlers-Danlos patients make up 5% of all aortic dissections, and half of all dissections in women younger than 40 years occur during the third trimester of pregnancy.[9]

Given that aortic dissection is relatively rare and can present in a multitude of various syndromes (acute CHF, MI, stroke, ischemic lower limb, paraplegia, gastrointestinal ischemia), it should not be surprising that accurate diagnosis remains elusive. One recent study of 66 patients with dissection found a misdiagnosis rate of 39%,[10] a number that has been consistent since the 1980s.[11] The most common misdiagnosis of aortic dissection in that study was acute coronary syndrome, also unchanged over the past 40 years.[12] This occurs not just because patients are having chest pain, but their ECGs can be suggestive of acute ischemia. In the IRAD (international registry of aortic dissection) database, only 31% of patients with dissection had normal ECGs.[13] ECG findings consistent with acute MI also are not rare in dissection.[14] One study found up to 22% of acute dissections had ECG findings suggestive of non-STEMI and 4% had STEMI findings.[15] The "needle in a haystack" concept is relevant. One author estimated that this translates into 25-200 cases of acute dissection with STEMI changes on the ECG in the entire United States annually, compared to the tens of thousands of patients with actual STEMIs.[16]

Patients with acute aortic regurgitation caused by the dissection will present with symptoms of acute CHF (dyspnea, pulmonary edema), and also may be misdiagnosed as such.

Besides misleading ECGs, the most specific cardiac enzyme for ischemia, troponin I, was found elevated in 23% of patients with aortic dissection as well.[17] Given the shared risk factors for both aortic dissection and coronary artery diseases in these patients, undoubtedly some of the patients with elevated troponin actually are experiencing cardiac ischemia as well as aortic dissection.[15] This further underscores the difficulty in accurately distinguishing the two conditions. The recent example of actor John Ritter, who died of a dissection at a California hospital on the way to the catheterization laboratory for presumed acute MI, emphasizes both how easy it is to confuse dissection with MI and how difficult it is for relatives to accept when "healthy" patients die suddenly in the ED.

Unfortunately misdiagnosing an aortic dissection as an acute MI can lead to disaster in several ways. Untreated mortality rates are quoted as 1% per hour[7] for the first 24–48 hours. One recent study found that patients with acute dissection treated for MI instead had similar mortality rates to untreated patients, with a case fatality rate of 71% for misdiagnosed patients.[10] The current standard treatment for acute MI involves several anticoagulants (heparin, aspirin, antiplatelet drugs) as well as thrombolytics. Administering these medications to patients with aortic dissection is associated with heightened risk via increased bleeding. In this study of patients misdiagnosed with ACS, 100% received aspirin, 85% heparin, and 12% fibrinolytic agents.[10] The pressures on ED staff to reduce door-to-drug times[18] coupled with the fact that hospitals often adopt pay-for-performance incentives to meet time-sensitive goals (antibiotics for pneumonia, aspirin for acute MI, etc.)[19] means that it may be more difficult for ED physicians to pause in treatment of suspected acute MI patients and take the time to rule out a dissection.

The question, then, is what items can the ED physician use to help identify the patients who need to have aortic dissection excluded as a diagnosis? While aortic dissections are too variable for any guidelines to be highly specific, the following demographics, signs, and symptoms can be helpful. Much of the data below come from the international registry of aortic dissection (IRAD — see www.iradonline.org). First, the mean age for presentation is 63 years,[13] and 68% of patients are men.[20] Severe and sudden onset of pain may be the most useful clinical feature of all. Patients described their pain as severe or "worst ever" in 91% of cases, and pain came to full strength from the onset in 85%.[13] Classic symptoms of "tearing" pain or migratory chest pain are more specific for dissection but occur less often. Only 50% described the pain as ripping or tearing, and pain was migratory in only 16%.[13] However, 64% of patients described the pain as "sharp."[13] Syncope in combination with acute chest pain is seen at similar rates in both MI and dissection (about 10%),[21,22] but is seen more often with proximal dissection and may indicate development of

Table 1: Avoid Misdiagnosing Acute Aortic Dissection as Acute MI*

High Risk Clinical Features:

- Sudden onset and/or tearing/ripping pain
  - Sudden onset in 85%
  - Only 50% describe as tearing/ripping
- Widened mediastinum on chest radiograph
  - Only 61% of patients have widened mediastinum
  - 12% of films are normal
- Pulse/blood pressure differences
  - 15–30% have pulse deficits
- Presence of all 3 findings seen in 83% of acute dissections
- Absence of all 3 seen in only 7% of acute dissections

Know the Risk Factors:

- History of hypertension
- Age > 60 years
- Male more often than female (68% vs 32%)
- For patients < 40 years old:
  - Marfan's syndrome
  - Ehlers-Danlos syndrome
  - Pregnancy (third trimester)
  - Bicuspid aortic valve
  - Cocaine — recent use

Tests Can Suggest Acute Cardiac Ischemia

- ECG:
  - 31% of ECGs are normal
  - Up to 26% will have ECG findings suggestive of AMI or ischemia
  - 22% of ECGs have non-STEMI changes
  - 4% have STEMI changes
- Troponin:
  - Up to 23% can have elevated troponin I

Diagnosis

- No reliable serum marker has yet been identified
- D-dimer levels > 400 ng/mL are seen in most dissections
- BUT it is not specific enough to rule out dissection if absent
- Chest CT, TEE, angiography, or MRI remain the definitive modalities for diagnosis

* References: 7, 13, 15, 17, 24, 25, 29

cardiac tamponade.[22] Thus, syncope with aortic dissection correlates with markedly increased mortality.[16]

Physical signs also can be suggestive of acute dissection. While hypertension is a well-established risk factor for aortic dissection, it is not consistently found on presentation. Of IRAD patients, only 35% of patients with proximal dissection had BP > 150 mmHg; however, 70% of distal dissections had hypertension.[13] Hypotension is an ominous finding associated with a substantially increased risk of death.[23] The most useful physical finding described is pulse deficits, defined as unilateral weakly palpated or absent pulses.[7] These can be detected on physical exam, e.g. an absent left carotid pulse, or by noting significant differences (> 20 mmHg)[24] comparing blood pressure of the extremities. Be aware that pulse deficits in patients with distal dissections may be present only in the legs and that pulse deficits may be transient.[7] Roughly 15–30% of patients will have pulse deficits,[13,25] thus stressing the importance of developing the habit of screening suspected acute MI patients for isolated absent pulses. When found, pulse deficits also correlate with higher in-hospital complications (coma, renal failure, limb ischemia) as well as higher mortality (44% vs. 25%).[25]

Diagnosis of acute aortic dissection can be confirmed only by one of four imaging studies: CT scan, TEE (transesophageal echocardiogram), angiography, or MRI. One may fortuitously see an intimal flap in the abdominal aorta using bedside ultrasound,[26] but typically one of these four studies is required to make the diagnosis. Chest radiographs can be helpful when they show findings suspicious for aortic dissection (widened mediastinum, displaced calcification, tracheal displacement), but one recent review of 109 patients found only a 67% sensitivity for dissection.[27] Plain film findings also were very non-specific. For example, more patients without dissection had tracheal deviation than those with the disease.[27] The IRAD database shows that only 61% of patients had a widened mediastinum and that 12% of chest radiographs were normal.[13]

Attempts have been made to identify serum markers that can be used to screen patients with chest pain to pull out those with dissections.[28] To date, the most accurate marker appears to be plasma D-dimer levels.[29] D-dimer levels > 400 ng/mL were found in a study of 94 patients with acute dissection to be 99% sensitive but only 34% specific.[29] Unfortunately, D-dimer levels are not precise enough to be used alone to rule out dissections; patients with thrombosed false lumens may be missed by D-dimer alone.[30] Patients with any high-risk feature (sudden tearing pain, pulse deficits, widened mediastinum, etc.) in their presentation should continue to undergo definitive imaging (CT scan, TEE, angiography, or MRI).[30]

The bottom line at this time is that

patients with chest pain atypical for dissection, ECGs suggestive of ischemia, and normal/nonspecific chest radiographs are more likely to be misdiagnosed or experience delayed diagnosis.[31] Other features identified as correlating with a delay of diagnosis were pleural effusion on chest radiograph and patients presenting with respiratory distress.[32] Overall, three high-risk features have been identified in retrospective analysis of patients with aortic dissection: sudden onset and/or tearing/ripping pain, widened mediastinum on chest radiograph, and pulse/blood pressure differences.[24] Aortic dissection was found in only 7% of patients without all three features, but 83% had all three.[24] One must remember these "classic" findings; unfortunately, cases where textbook presentations have been missed are not that rare.[33]

At centers with emergency angioplasty, the push to keep door-to-balloon times under 90 minutes can be beneficial for patients with dissection instead of MI. Patients taken rapidly to the catheterization laboratory from the ED with minimal work-up can have their dissection quickly identified by aortogram. The disadvantage is that they may be more likely to be given anticoagulants. Patients who are given tPA, such as those being transferred from smaller hospitals to those with intervention cardiology, are likely at higher risk from misdiagnosis. Clearly it is not constructive to obtain CT scans of every patient with an acute MI to rule out dissection. Besides the time delay, increased dye load from both CT scan and cardiac catheterization undoubtedly would cause more cases of acute renal failure than diagnosis of acute dissections. See Table 1 for suggestions on minimizing misdiagnosis.

Pulmonary Embolism. While acute pulmonary embolism (PE) may be confused less often with acute MI, there are certainly more acute PEs than aortic dissections, giving greater opportunity to misdiagnose PE as an MI. PE is the number three killer in the United States, with an estimated 50,000-100,000 deaths per year.[34] It is difficult to obtain precise numbers, as many PEs are diagnosed only on autopsy and perhaps as many as 50% of these are not even suspected antemortum.[35] On the other hand, the prevalence of PE is only 25-35% in patients who are evaluated by physicians for PE.[36] Thus, the unhappy reality is that physicians are looking hard for PE largely in patients who do not have the condition, and "missing" it in those who do. One must wonder how so many PEs can go undetected if ED physicians are searching so diligently that up to 75% of patients are screened for PE do not have the diagnosis.

The answer may be that most of the PEs not detected by physicians may be clinically silent; thus, many PEs are not found because the patients with them are not presenting for medical evaluation. Studies in which VQ scans were done on all patients with proximal DVT found that 40-50% of them had silent PEs.[37] While many of these silent PEs were silent for a reason (they were minor and had no clinical impact), nearly 6% of the silent PEs consisted of > 6 perfusion defects.[37] Younger patients can obstruct up to 50% of their pulmonary tree, yet remain asymptomatic.[38] Given the fact that a large percentage of DVTs are also silent (up to 80% of patients with PE have silent DVT),[39] this implies that many patients are not presenting for care or are not developing symptoms that permit diagnosis. Thus, asymptomatic PEs are 4-5 times more common than symptomatic ones,[40] leading at least one author to state, "There can only be a limited advantage to encourage increased alertness for a disease that is usually asymptomatic."[41] However, this is not to undermine the importance of accurate diagnosis when patients do come to the ED with PE. Mortality from untreated PE can be 15-25% compared to 5% in treated patients.[42]

Multiple risk factors for PE have been identified (immobility, recent trauma/surgery, presence of cancer, hormone/birth control therapy, obesity, etc.), but one may not appreciate that elderly patients, especially those with chronic obstructive pulmonary disease (COPD) or congestive heart failure (CHF) also are at higher risk for PE.[43] Be aware of acute dyspnea in these patients that differs from prior exacerbations. The overall mean age for presentation with a PE is 60 years, and PE occurs 10 times more often in patients older than 75 years compared to those younger than 40 years.[44] Age may be an independent risk factor or it may just be that older people are more likely to have recent surgery and underlying disease states (i.e., lung cancer) that predispose them to DVT and PE. Regardless, given the fact the acute MI and PE are both especially difficult to diagnose in elderly patients, this population is likely most at risk for misdiagnosis in the ED.

Clinical presentation of PE tends to separate into three categories: massive PE with circulatory collapse, small PE with minimal to no symptoms, and moderate PE with variable degrees of chest pain and dyspnea.[34] Patients with moderate PE may be at highest risk for misdiagnosis as acute MI. Their symptoms of dyspnea may be attributed to an anginal equivalent, and chest pain descriptions can be vague or described as "sharp," a term used by 20% of patients with PE[45] and 22% of patients with acute MI.[3] Be aware that syncope is a presenting symptom in up to 13% of patients with PE[46] but is much less common for acute MI (< 1%).[47,48]

ECGs can be helpful when signs of acute right heart strain are present (S1Q3T3 or new RBBB), but these findings can be transient.[49] Further, up to 27% of ECGs are normal in acute PE.[50] The most common ECG findings of all are sinus tachycardia and non-specific ST-T wave changes,[51] which are not useful for diagnosis. Several ECG patterns are known to occur with PE that can mimic acute MI. Right bundle branch block (RBBB) can be associated with ST segment elevation/depression and upright T waves in lead V1 and V2, thus simulating anterior or posterior MI patterns.[52] More commonly, the ECG will show ST segment depression and inverted T waves in leads III, V2, and V3, a pattern that is not a typical anatomic distribution for acute MI. Other studies have show T wave inver-

Table 2: Avoid Misdiagnosing Acute Pulmonary Embolism as Acute MI*

High Risk Clinical Features:

- Sudden-onset of dyspnea combined with syncope
  - However, 50% do not have sudden onset
- Elderly patient
  - PE seen 10 times more often in those > 75 years of age
- History of PE risk factors
  - Recent surgery
  - Immobility
  - Obesity
  - Cancer
  - COPD
  - CHF
  - Previous MI

Tests Can Suggest Acute Cardiac Ischemia

- ECG:
  - 27% of ECGs are normal in PE
  - T wave inversions in leads III and V1 are associated with PE rather than myocardial ischemia
  - Remember ECG findings of S1Q3T3 and RBBB may be transient
- Troponin:
  - Up to 45% can have elevated troponin I (< 4–5 ng/dL)
  - Is a marker of right heart strain

Diagnosis

- Negative D-dimer levels rule out PE in LOW risk patients only
- Beware of negative chest CT for PE when patient is high risk
  - PIOPED II suggests VQ scan to confirm
- Treatment is effective
  - Mortality reduced from 25% to 5%

* References: 42-44, 49, 50, 53, 56, 57

sions in inferior and anterior leads,[52] which easily could simulate myocardial ischemia. However, one study looked specifically at differences in T wave inversion in patients with ACS and those with acute PE. They found that only 1% of patients with ACS had inverted T waves in leads III and V1, but these changes were seen in 88% of patients with PE.[53] Although this study only included 40 patients with PE and 87 patients with ACS, these ECG differences could be helpful if validated in a larger group. Remember, though, that as with acute dissection, some of these patients actually may have cardiac ischemia as a complication of PE, making it even harder to render an accurate diagnosis.

Troponin levels also can be misleading. Several studies have noted that troponin I levels are elevated in 32%[54] to 45%[55] of patients with PE. Troponin levels tend to be mildly elevated and usually are less than 4-5 ng/dL.[56] These patients tend to have moderate to massive PEs, and troponin levels appear to result from increased right heart strain. Elevated troponin levels in acute PE are associated with higher complication rates, cardiogenic shock, and increased mortality.[56] D-dimer levels are known to be elevated in acute PE, but they are not specific enough and generally are limited to ruling out PE in low-risk patients only.[43] PIOPED II shows at least 15% of patients with high suspicion of PE will have a negative D-dimer.[57] Conversely, D-dimer levels also can be elevated in acute MI,[58] but D-dimer levels have not been consistently shown to be helpful in diagnosing acute MI.[59,60]

The bottom line in these patients is to remember that mildly elevated troponin levels combined with T-wave inversions on the ECG do not necessarily diagnose the patient with an acute MI. T wave inversions that do not follow expected patterns for coronary ischemia, such as isolated inversions in leads III and V1, are more indicative of PE than MI. Be especially vigilant for PE when these findings occur in elderly patients with history of COPD or CHF. In addition, PIOPED II data show that chest CTs are negative in up to 18% of patients with high suspicion of PE.[57] Table 2 provides a summary of tips for distinguishing acute MI from PE.

Benign Conditions Confused with Acute MI

GERD (Gastroesophageal Reflux Disease). (*See Table 3.*) The classic dilemma of differentiating pain of cardiac ischemia from that of heartburn shows how much the two conditions can overlap. Overall, indigestion is probably the most common misdiagnosis of STEMI patients.[61] One study found that 58% of patients discharged after admission for possible ACS were found to have esophageal dysfunction instead.[62] Reflux also is very common; as reported in one study, heartburn occurred in 7% of patients daily, 14% of patients weekly, and 15% of patients monthly.[63] This totals 36% of patients experiencing reflux symptoms at least once a month, and it is estimated that 60% of adults will have at least one episode in their lifetime.[64]

It is easy to see why it can be hard to tell the two apart. Chest pain in GERD can be a dull burning sensation or can be ischemic-sounding with a squeezing chest pain associated with nausea, vomiting, and diaphoresis. One study found that squeezing chest pain was described as often as burning pain in patients with reflux.[3] Radiation of pain to the neck, jaw, shoulders, back, and arms also is seen with GERD.[64] Both chest pain from GERD and from angina have been reported as relieved by belching.[65] Reflux also can be precipitated by

Table 3: Common Misdiagnoses for Acute MI*

GERD

- Often described as a "squeezing" chest pain
- Associated symptoms of diaphoresis, nausea, vomiting also common
- Can radiate to neck, jaws, shoulders, back and arms
- Risk factors: diabetes, tobacco use, obesity
- Nitroglycerin commonly relieves reflux pain
  - Antacids also can relieve pain of acute MI
- Useful identifying features of GERD
  - Acid refluxing into mouth
  - Water brash (brief hypersalivation)
  - Symptoms are positional — worse bending and lying down
  - Often triggered by large, spicy meals
  - Tend to be chronic in nature (occurring for years)

Musculoskeletal Chest Pain

- Pleuritic pain lowers risk of acute MI, but does not rule it out
  - Seen in 13–15% of acute MI patients
- Pain reproduced by palpation lowers risk, does not rule out MI alone
  - Seen in 7–15% of acute MI patients
- History of PE risk factors
  - Recent surgery
  - Immobility

Anxiety

- Can present with acute chest pain, SOB, palpitations
- Beware as dyspnea can be the chief complaint in acute MI
  - 13–33% of acute MI patients present with dyspnea
  - Dyspnea is the number one complaint in elderly patients with MI

* References: 64, 67-69, 70, 73, 74, 80, 81

exertion and relieved by rest or precipitated by emotional upset. Diabetes, obesity, and tobacco use are common risk factors for development of GERD, as they are associated with esophageal dysmotility. Abdominal pain also is a common chief complaint in acute MI patients who present without typical chest pain and is second only to dyspnea.[66] Overall, however, abdominal pain is a relatively rare chief complaint of patients presenting with acute MI.[67] When it does occur, though, it often is from inferior MIs in younger male patients, the same patient group that frequently complains of reflux symptoms.

Further complicating the picture, relief of symptoms with nitroglycerin is not helpful to identify anginal pain. In a study of 251 ED patients with chest pain, 88% of those with cardiac chest pain had some relief with sublingual nitroglycerin, but so did 92% of those with non-cardiac chest pain.[68] Another study confirmed these numbers and again found more patients without cardiac chest pain had relief with nitroglycerin (41%) than those with coronary disease (35%).[69] Likewise, relief with antacids is well described in both reflux and patients with proven myocardial ischemia.[70] Be careful not to use the patient's response to these treatments as decision points in their evaluation.

Fortunately, there are a few features of GERD that, when present, can help distinguish it from angina. GERD more typically is associated with reflux of acid into the mouth and/or water brash, described as a hypersalivation that produces up to 10 mL in less than 1 minute.[64] Reflux symptoms can be positional, meaning they are worse with bending over or lying down. They often are triggered by meals, especially larger meals, or spicy/hot foods. The fact that 36% of adults may have reflux symptoms monthly means that most patients with GERD are likely to have had similar symptoms chronically. Patients who have had reflux well documented in the past who describe their symptoms as such are less likely to be suffering from a new condition. Likewise, patients with a history of documented angina are more likely to describe their MI pain as a much more intense version (i.e., a similar location and feeling) of their previous angina. Identifying these components of the history underscores how important it can be for the ED physician to be thorough. Detecting these features can help support the diagnosis of GERD. Ultimately, history alone will not rule out MI in most patients.[71] It must be emphasized that changes in a patient's reflux symptoms prompting a visit to the ED when he or she has not presented in the past should be taken seriously, and further evaluation likely is indicated.

Musculoskeletal Chest Pain. Chest pain resulting from musculoskeletal sources is a very common reason for patients to seek medical care. A large study of more than 24,000 outpatient visits found it to be the number one diagnosis in these patients, causing 49% of the visits, compared to only 12% being due to coronary artery disease.[72] While chest pain that is pleuritic or reproduced by deep breaths is less likely to be cardiac in origin, this finding alone does not rule it out.[73] Older studies have reported that pleuritic pain was seen in 15% of patients with acute MI.[74] More recent ones have found that a similar number of patients with acute MI (13%) did have a component of their pain described as pleuritic, but none of the patients whose pain was entirely pleuritic had active coronary disease.[73]

Reproducibility of the patient's pain by palpation of the chest wall has been presented in the past as strong evidence that the pain's source is not

due to coronary disease.[75] This aspect of the physical examination also is used in well known protocols used to identify patients with acute MI in ED patients.[76] More recent studies have confirmed that a small percentage of patients with acute MI will have this feature (7-15%),[73,74] but this number remains high enough that one should not use reproducibility of pain by palpation as a reliable single feature to rule out possible MI.

Anxiety. Anxiety disorders are familiar to seasoned ED physicians and are some of the most common psychiatric disorders. It is estimated that up to 25% of the U.S. population suffers from pathologic anxiety during their lifetime.[77] In the ED, one must be careful when attempting to diagnose a new-onset anxiety disorder. Up to 42% of patients presenting with apparent anxiety disorders are later found to have organic disease instead.[78] Conversely, anxiety disorders are seen in up to 30% of patients initially presenting with chest pain who later are diagnosed as non-cardiac chest pain.[79]

Symptoms of anxiety include hyperventilation, feeling short of breath, palpitations, chest pain — complaints that can be consistent with acute MI as well. Patients presenting with an anxiety attack feel impending doom and experience intense hyperventilation. When these patients roll into the ED, it often takes some serious thought as to whether they may be right when they breathlessly state "I'm going to die!" Indeed, dyspnea is a common complaint in acute MI patients, especially elderly ones. Dyspnea has been shown to be the single most common complaint for acute MI in patients older than 85 years.[80] In older studies, dyspnea is present in 33% of patients with acute MI,[81] but more recent work still shows dyspnea in 14% of acute MIs and in 5% of patients with unstable angina.[67] However, another study of unstable angina found that dyspnea was seen in 69% of patients.[82]

In general, anxiety disorders tend to occur in females twice as often as males, and the average age of onset is in the third decade. Unfortunately, this may only confuse the picture, as younger patients and women are among the groups where MI most often is missed. When treating acute anxiety in the ED in patients where the diagnosis is not clear, further evaluation to screen for acute MI often is needed.[83]

The Patient with Recent Stress or Catheterization

When patients present to the ED with chest pain and a history of known coronary disease, the decision of whether to admit the patient can be challenging. While it may seem on the surface that these patients would be an automatic admission, in real life this is not always what happens. The patient is not always experiencing another acute MI or unstable angina, and if it is safe to do so, then the patient should be discharged. The ED physician must risk stratify these patients further into those who truly need admission and those who can be safely discharged. Many factors go into this decision, but this section will focus on the patient's previous cardiac testing (stress tests and cardiac catheterization) and the limits of these tests. Specifically, if a patient has had a recent catheterization (< 6-12 months) that is either normal or stable from previous studies, does this information help one to decide his or her disposition? The same question using recent stress tests also will be addressed. Likewise if the patient has had a recent negative stress or catheterization, how useful is this information?

At least two recent studies have addressed this issue, and the results were somewhat surprising in that history of a recent negative work-up did not appear to influence subsequent ED evaluations.[84,85] One study looked at the utilization of resources in the year following an admission for chest pain that resulted in a non-cardiac diagnosis.[85] Researchers followed 556 patients admitted for chest pain, 116 of whom had a negative stress test and 20 of whom had negative cardiac catheterizations. There was no difference in use of resources in the next year, defined as echocardiograms, stress tests, or catheterizations, between the study patients or controls.[85] Another study examined patients with any history of negative stress tests and looked for an influence on the ED physician's decision to admit the patient.[84] They also found no impact on admission rates but did not discriminate between patients with recent stress tests and those whose studies were several years old. As expected, patients with a previous abnormal stress test were admitted more frequently.[84]

In addition, as observation units or chest pain units are being used in increasing numbers for risk stratification of chest pain patients in the ED, emergency physicians are at times in charge of choosing which stress test to perform and managing the results. Therefore, overall limits of stress testing will be discussed as well. Ultimately, one should remember that if the patient has been evaluated recently by a cardiologist, one can always consult him or her for help in deciding difficult dispositions.

Recent Stress Test. Currently, most stress tests performed have two components: the classic treadmill or exercise part and the subsequent nuclear perfusion study. The treadmill test is performed by attaching an ECG monitor to a patient using a treadmill or stationary bicycle. If the patient is physically unable to walk on a treadmill or ride the bike, medications can be used to increase their heart rate instead (persantine or dobutamine). The most common protocol is the Bruce protocol, where resistance is increased in 3-minute intervals[86] until the patient reaches a predetermined level, such as a maximum metabolic output or through physiological signs of stress (drop in blood pressure, angina, drop in skin temperature, or cyanosis). The ECG is monitored during exercise and recovery to identify ST segment depression or elevation indicating ischemic changes. Contraindications for exercise testing are listed in Table 4. The second part is the perfusion study, which is performed by injection of an isotope (thalium-201, or technetium-99 sestamibi) that allows one

Table 4: Exercise Testing and Perfusion Studies*

Contraindications

- Absolute
  - Unstable angina
  - Evolving ECG changes
  - Abnormal cardiac biomarkers
  - Significant CHF
  - Significant aortic stenosis
  - Severe hypertension (> 200 mmHg systolic, > 110 mmHg diastolic)
  - Clinical indication that coronary angiography is needed
- Relative
  - Valvular heart disease, anemia
  - Interventricular conduction delays (including bundle branch blocks)
  - Hypokalemia
  - Hypoxia or volume overload
  - Beta blocker use

Limits of Utility

- Exercise test
  - Baseline ECG changes make interpretation difficult
  - False positive results common in patients with relative contraindications
  - Most useful for patients with intermediate risk of disease
- Perfusion study
  - Can miss global ischemia (left main, 3-vessel disease)
  - Microvascular disease can simulate large vessel disease

Prognostic Value

- Sensitivity/specificity
  - 68% and 77% for exercise stress
  - 90% and 70% for perfusion
  - Numbers for both tests are in terms of ability to detect coronary lesions with > 50% obstruction
- Negative tests do NOT mean absence of coronary disease, but do help predict patients at risk for near-term cardiac events (MI/death)
- Perfusion study numbers hold up for 2 years into future
  - Normal study = 0.4% risk of MI/death per year
  - Multiple abnormal segments = 9% risk of MI/death per year

* References: 87-90

to assess cardiac perfusion during and after exercise. One can compare the exercise and rest images to identify areas of the heart that are not perfused normally only during exercise (reversible ischemia) or not at all (scarring).

As with any test, certain factors can make the test difficult to interpret or reduce its accuracy. For the standard exercise component, patients must have relatively normal baseline ECGs from which one can interpret transient ischemic changes. Patients with left ventricular hypertrophy or digitalis therapy often have baseline ST segment depression, making ECG changes harder to detect. Other conditions commonly associated with false-positive treadmill test results include valvular heart disease, anemia, interventricular conduction delays (including bundle branch blocks), hypokalemia, and significant hypoxia or volume overload.[87] Results are reported in general as negative or positive for ECG changes suggestive of ischemia.

Overall, exercise testing is most useful when performed in populations who are at intermediate risk of coronary disease.[88] The positive predictive value is high (98%) in patients suspected to have coronary disease and, likewise, the negative predictive value is also high (98%) in patients unlikely to have coronary disease.[88] Thus an exercise test alone does little in screening very high risk or very low risk patients. It is best used in intermediate populations where the overall sensitivity and specificity are 68% and 77%, respectively.[89] In general, contraindications for stress testing of emergency department patients include those with evolving ECG changes, abnormal cardiac biomarkers, worsening or persistent chest pain, and clinical risk profile that suggests coronary angiography is needed.[87]

In most hospitals, the exercise test is performed in conjunction with nuclear perfusion imaging studies (stress myoview, stress thallium). Images taken during and after exercise show general blood flow to the heart, and areas that do not increase flow during exercise indicate possible ischemia. Images are obtained using single-photon emission computed tomography (SPECT). Again, detecting areas of reversible ischemia indicate regions at risk for future MI. The overall sensitivity and specificity of perfusion studies is 90% and 70%, respectively.[90] Since the study relies on comparison of muscle perfusion with the adjacent "normal" areas, perfusion studies have some inherent inaccuracy. False-negative results are seen in patients with overall low perfusion, such as in left main disease or proximal 3-vessel disease. They can be missed as the entire heart is not well perfused and no single area will stand

Table 5: The Patient with Recent Cardiac Catheterization (< 6-12 months)*

Recent Stent Placement

- Patients must stay on aspirin/clopidogrel (Plavix) for 6–12 months or longer after placement of drug-eluting stent
  - High risk of re-stenosis and STEMI if non-compliant
  - Currently recommended to stay on aspirin therapy for life
- Diabetics have twice the risk of re-stenosis compared to non-diabetics

Recent Negative Catheterization

- Verify results when patients report them as "negative"
  - Truly negative = no evidence of disease
  - Patient may only mean no intervention was required
- Patients with negative catheterization still can have acute MI
  - Coronary spasm (Prinzmetal angina, cocaine)
  - Bridging vessels — dive into muscle instead of staying on surface and are compressed in systole
  - Microvascular disease
  - Subendocardial ischemia with severe LVH
- Negative catheterization does not rule out all coronary disease, but patient is at lower risk than those not yet studied
  - 96% survival rate for 7 years with negative catheterization
  - 92% survival rate for 7 years with mild lesions (<50%)
- Patient with "good story" for angina and multiple risk factors should still be evaluated for possible AMI or USA
  - Cath = lumenogram
  - Can have extralumenal coronary lesions which can still produce AMI

* References: 95, 101, 104, 106, 112

out as different. Also not all perfusion differences are caused by large-vessel coronary disease. Patients with microvascular disease (diabetes, hypertension, and hyperlipidemia) may have significant flow imbalances without obstructive large-vessel lesions. Breast implants also can make the study more difficult to interpret.

Documentation of a recent perfusion study can be more helpful with patient disposition than a simple exercise test. The extent of the perfusion defect directly correlates to the patient's risk of MI or death. Patients with normal perfusion studies have only a 0.4% risk of MI/death per year compared to a 9% risk for those with multiple abnormal segments.[91] Large studies (21,000 patients) have confirmed these numbers, and one 6-year follow-up survey still found an annual rate of MI/death of 0.88%.[92] Even patients with known coronary disease have a low annual risk (0.9%) of MI/death when the perfusion study shows no reversible ischemia. Thus current cardiology texts state that a normal perfusion study can be used to predict a low risk of MI/death for as far as two years into the future (the "warranty period").[93] Keep in mind, though, that the specificity and sensitivities quoted above are for the detection of coronary lesions > 50%, as this is the cut-off for the definition of coronary artery disease in most cardiology literature; some even use a level of > 70%.[93] Thus, exercise tests and perfusion studies do not rule out the presence of coronary disease; they simply identify patients at risk of future events (i.e., those likely to have significant obstructing lesions).

Recent Cardiac Catheterization (< 6–12 months). The first cardiac catheterization on a living patient occurred in 1929 in Germany, when a surgical apprentice performed the procedure on himself. Even though Dr. Forssmann was later awarded the Nobel Prize for his work in 1956, at the time, he was fired for doing the unauthorized procedure. Selective coronary angiography began in 1958, and the first balloon angioplasty was done in 1974. In 1997, there were roughly 1 million cardiac catheterizations in the United States alone, and this number has climbed to 2.5-3 million in 2008.[94] Besides defining coronary disease, a cardiac catheterization provides information on left ventricular dysfunction, measures pressures and cardiac output, and can assess valvular problems.

Multiple factors go into assessing a patient's risk using catheterization results. Patients with coronary lesions generally will be classed as having single-, double-, or three-vessel disease. When patients with coronary artery disease undergo catheterization, approximately 25% will have either single-, double-, or triple-vessel disease, defined as at least a 70% narrowing.[95] Another 5–10% will have left main disease, and the remaining 15% will have no critical lesions (> 70% stenosis). Statistically, the more vessels involved, the higher the risk of future MI. The 5-year survival rate for patients with triple-vessel disease and a 95% proximal LAD lesion is 59%, compared to 93% for a patient with only low-grade single-vessel disease when both are treated medically.[96] Even asymptomatic patients with triple-vessel disease experience 4-5% annual mortality.[97]

Patients with documented coronary artery disease on a previous catheterization who did not require intervention at the time are obviously at risk of future events. Most cardiologists only place stents in lesions with least 70% or greater stenosis, but they may stent a 50–70% lesion if the patient is experiencing unstable angina due to a particular lesion. The decision to place a stent can be complicated, as lesions are believed to need to be at

least 95% or greater to be responsible for most rest angina, but only 15% of acute MIs arise from lesions > 60%.[98] Thus, many patients will have previous catheterization reports documenting lesions less than 50% who are being medically managed.

Ultimately, one either may admit patients with chest pain and history of coronary disease, place them in a chest pain unit setting, or discharge them after serial biomarkers to rule out infarction. Patients who have a "good story" for their angina or who rarely seek care for their chest pain usually are better off being admitted negative biomarkers or not, and patients who are able to be discharged usually are those who are evaluated often for chest pain that turns out not to be MI or unstable angina or who are well known to their cardiologist. Discussion with the patient's cardiologist is advised before discharging for any help with the decision and to ensure timely follow up.

Recent Stent Placement. Coronary stents were introduced in the late 1990s as a solution to the high rate of restenosis (30-40% in only 6 months) seen in balloon angioplasty alone.[99] Originally, bare metal stents were used, but these were associated with a 20-30% restenosis rate in 6-9 months due to intimal hyperplasia[99] and caused angina in up to 15% of patients in 1 year after deployment.[100] Subsequently, drug-eluting stents were developed in 2001 using agents released by the stent to reduce the extent of intimal hyperplasia.[101] Drug-eluting stents (DES) have been successful in reducing the rate of restenosis down to only 4-6% and, as a result, 90% of all stents placed in the United States and Europe now are DES. However, patients given DES must be on a much longer regimen of aspirin and clopidogrel (Plavix) of up to 6–12 months or longer.[101] Even after this treatment, they also must remain on an aspirin regimen for life.[102] Current work with bioresolvable stents is likely to be the next development and may help improve outcomes even further.[103]

ED physicians need to be aware that certain groups of patients are at increased risk of complication after stent placement. (*See Table 5.*) Patients with a history of diabetes are at higher risk for restenosis leading to re-intervention, with double the rates of non-diabetics.[104] Those who stop taking their aspirin and clopidogrel after stenting also are at increased risk for late-stent thrombosis, defined as occurring more than 30 days after stenting.[101] Late-stent thrombosis is a dangerous event and is associated with a 45% mortality rate.[105] Patients who have had stent placement in the last several months should be specifically asked if they are taking their clopidogrel, as they are at much higher risk for acute MI if they have stopped. All patients with DES also should be asked to verify that they have been compliant with their aspirin therapy. Patients in these higher risk categories should be discussed with their cardiologist.

The "Negative" Catheterization Result. Unfortunately, when the patient's history reveals negative catheterization results, one still must proceed with caution. (*See Table 5.*) First, beware of the patient's version of the catheterization results. One should verify that the results truly were negative for coronary lesions, as many times when the patient says "negative" it may be that coronary disease was indeed found but no intervention/stenting was performed. In other words, negative to a physician means no coronary artery disease was found, but to the patient, it may mean no action was required that day for the 40% proximal LAD lesion.

Secondly, a truly negative catheterization result does not mean the patient could not be having an acute MI now. Coronary spasm easily can cause a fatal STEMI and can occur in multiple ways. Prinzmetal angina was first described by Dr. Prinzmetal in 1959 to explain a syndrome in which patients had normal exercise tolerances but developed acute MI/angina at rest, often in the early morning hours.[106] Coronary vasospasm is thought to be due to dysfunctional coronary endothelium or release of local vasoconstrictors from platelets (serotonin or thromboxane A2).[107] Cocaine also is a well-established cause of coronary vasospasm.

Myocardial bridging is another mechanism by which MI still can occur in patients with negative catheterization. This term refers to a large coronary vessel that usually is epicardial but that goes under the myocardial surface for short segments. This can cause physical compression of a coronary vessel by the surrounding muscle during systole. While seen in only about 5% of patients with normal vessels,[95] the incidence in autopsy series is quoted between 15–85%.[108] Bridging most often occurs in the middle segment of the LAD. A recent IVUS study suggested that the phenomenon is more frequent after all. The study found an incidence of 23%, but this was in a patient population with a high incidence of artery disease, suggesting that most bridging lesions are angiographically silent.[109]

Negative catheterization results are seen in up to 20% of patients referred for clinical suspicion of angina.[95] Far more women (50%) than men (17%) with suspected angina have negative results or lesions < 50%.[110] Even 10% of women and 6% of men who present with STEMI have no disease or only non-obstructing lesions.[111] Some of these patients who have typical angina-sounding symptoms, multiple coronary risk factors (hypertension, diabetes, elevated cholesterol, abdominal obesity), and ST segment depression on exercise ECGs are referred to by cardiologists as "cardiac syndrome X."[112] The source of the patients' pain has been debated in the past, but newer studies suggest they are experiencing subendocardial ischemia.[113] This occurs not from large-vessel obstructions, but from very small vessel flow limitation or microvascular angina.[95] In the past, prognosis of these patients was thought to be excellent. At least one recent study found that in patients in whom microvascular angina could be demonstrated, 14% had either cardiac death, MI, or CABG in a 28-month period.[114]

Finally, patients who have significant left ventricular hypertrophy also can develop mild, diffuse subendocar-

dial ischemia. Essentially, the heart muscle becomes thick enough that the blood supply to the subendocardium cannot keep pace with demand. In times of increased demand, small areas can infarct but subsequent catheterization will reveal no blockage.

The bottom line is that most patients who have had truly negative catheterization in the recent past (< 6-12 months) are less likely to be infarcting than someone whose arteries have not been studied. However, the above scenarios do happen, and a negative catheterization alone does not rule out the possibility of an acute MI. Anyone who has multiple risk factors, especially diabetes and smoking history, who presents with a "good story" for angina still should be evaluated for possible acute MI or unstable angina. Overall, patients with negative catheterization reports have a low mortality rate. A study of survival rates for patients with normal catheterizations found that 96% were alive after 7 years, compared to 92% of patients who had mild coronary lesions (< 50%).[112]

References

1. Pope JH, Aufderheide TP, Ruthazer R, et al. Missed diagnoses of acute cardiac ischemia in the ED. *N Engl J Med* 2000;342:1163-1170.
2. Lee TH, Goldman L. Evaluation of the patient with acute chest pain. *N Engl J Med* 2000;342:1187-1195.
3. Schor S, Behar S, Modan B, et al. Disposition of presumed coronary patients from an emergency room. A follow-up study. *JAMA* 1976;236:941-943.
4. McCarthy BD, Beshansky JR, D'Agostino RB, et al. Missed diagnoses of acute myocardial infarction in the emergency department: Results from a multicenter study. *Ann Emerg Med* 1993;22:579-582.
5. Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics—2008 update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2008;117:e25-146.
6. Klompas M. Does this patient have an acute thoracic aortic dissection? *JAMA* 2002;287:2262-2272.
7. Isselbacher EM. Diseases of the aorta. In: Libby P, Bonow RO, Mann DL, et al, eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 8th ed. Philadelphia, PA: Elsevier; 2008: 1457-1487.
8. Hatzaras IS, Bible JE, Koullias GJ, et al. Role of exertion or emotion as inciting events for acute aortic dissection. *Am J Cardiol* 2007;100:1470-1472.
9. Williams GM, Goh VL, Brawley RK, et al. Aortic disease associated with pregnancy. *J Vasc Surg* 1988;8:470-475.
10. Hansen MS, Nogareda GJ, Hutchison SJ. Frequency and inappropriate treatment of misdiagnosis of acute aortic dissection. *Am J Cardiol* 2007;99:852-856.
11. Spittal PC, Spittal JA Jr, Joyce JW, et al. Clinical features and differential diagnosis of aortic dissection: Experience with 236 cases (1980 through 1990). *May Clin Proc* 1993;68:642-651.
12. Viljanen T. Diagnostic difficulties in aortic dissection. *Ann Chir Gynaecol* 1986;75: 328-332.
13. Hagan PG, Nienaber CA, Isselbacher EM, et al. The international registry of acute aortic dissection (IRAD): New insights into an old disease. *JAMA* 2000;283;897-903.
14. Hirata K, Kyushima M, Asato H. Electrocardiographic abnormalities in patients with acute aortic dissection. *Am J Cardiol* 1995;76:1207-1212.
15. Biagini E, Lofiego C, Ferlito M, et al. Frequency, determinants, and clinical relevance of acute coronary syndrome-like electrocardiographic findings in patients with acute aortic syndrome. *Am J Cardiol* 2007;100:1013-1019.
16. Haro LH, Krajicek M, Lobl JK. Challenges, controversies, and advances in aortic catastrophes. *Emerg Med Clin North Am* 2005;23:1159-1177.
17. Bonnefoy E. Significant of serum troponin I elevation in patients with acute aortic dissection of the ascending aorta. *Acta Cardiol* 2005;60:165-170.
18. Bradley EH, Herrin J, Wang Y, et al. Door-to-drug and door-to-balloon times: Where can we improve? Time to reperfusion therapy in patients with ST segment elevation myocardial infarction (STEMI). *Am Heart J* 2006;151:1281-1287.
19. Sikka R. Pay for performance in emergency medicine. *Ann Emerg Med* 2007;49: 756-761.
20. Nienaber CA, Fattori R, Mehta RH, et al. Gender-related differences in acute aortic dissection. *Circulation* 2004;109: 3014-3021.
21. Canto J, Fincher C, Kiefe C, et al. Atypical presentations among Medicare beneficiaries with unstable angina pectoris. *Am J Cardiol* 2003;91:118-119.
22. Nallamothu BK, Metha RH, Saint S, et al. Syncope in acute aortic dissection: Diagnostic prognostic, and clinical implications. *Am J Med* 2002;113:468-471.
23. Tsai TT, Bossone E, Isselbacher EM, et al. Clinical characteristics of hypotension in patients with acute aortic dissection. *Am J Cardiol* 2005;95:48-52.
24. von Kodolitsch Y, Schwartz AG, Nienaber CA. Clinical prediction of acute aortic dissection. *Arch Intern Me*d 2000;160: 2977-2982.
25. Bossone E, Rampoldi V, Nienaber CA, et al. Usefulness of pulse deficit to predict in-hospital complications and mortality in patients with acute type A aortic dissection. *Am J Cardiol* 2002;89:851-855.
26. Fojtik JP, Costantino TG, Dean AJ. The diagnosis of aortic dissection by emergency medicine ultrasound. *J Emerg Med* 2007; 32:191-196.
27. von Kodolitsch Y, Nienaber CA, Dieckmann C, et al. Chest radiography for the diagnosis of acute aortic syndrome. *Am J Med* 204;116:73-77.
28. Mir MA. Aortic dissection — in pursuit of a serum marker. *Am J Emerg Med* 2008;26:942-945.
29. Ohlmann P, Faure A, Morel O, el al. Diagnostic and prognostic value of circulating D-dimers in patients with acute aortic dissection. *Crit Care Med* 2006;34: 1358-1364.
30. Sutherland A, Escano J, Coon TP. D-dimer as the sole screening test for acute aortic dissection: A review of the literature. *Ann Emerg Med* 2008;52:339-343.
31. Raghupathy A, Nienaaber CA, Harris KM, et al. Geographic differences in clinical presentation, treatment, and outcome in type A acute aortic dissection (from the IRAD). *Am J Cardiol* 2008;102: 1562-1566.
32. Rapezzi C, Longhi S, Graziosi M, et al. Risk factors for diagnostic delay in acute aortic dissection. *Am J Cardiol* 2008; 102:1399-1406.
33. Rogers RL, McCormack R. Aortic disasters. *Emerg Med Clin North Am* 2004;22: 887-908.
34. Goldhaber SZ. Pulmonary embolism. In: Libby P, Bonow RO, Mann DL, et al, eds. *Braunwald's Heard Disease: A Textbook of*

Cardiovascular Medicine, 8th ed. Philadelphia, PA: Elsevier; 2008: 1863-1879.
35. Pineda LA, Hathwar VS, Grant BJ. Clinical suspicion of fatal pulmonary embolism. *Chest* 2001;120:791-795.
36. PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism: Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). *JAMA* 1990;263:2753-2759.
37. Meignan M, Rosso J, Gauthier H, et al. Systematic lung scans reveal a high frequency of silent PE in patients with proximal DVT. *Arch Intern Med* 2000; 160:159-164.
38. Riedel M. Diagnosing pulmonary embolism. *Postgrad Med J* 2004;80: 309-319.
39. Buller H, Sohne M, Middeldorp S. Treatment of venous thromboembolism. *J Thromb Haemost* 2005;3:1554-1560.
40. Egermayer P, Town GI. The clinical significance of pulmonary embolism: Uncertainties and implications for treatment—a debate. *J Intern Med* 1997;241: 5-10.
41. Egermayer P. Silent pulmonary embolism. *Arch Intern Med* 2000;160:2218.
42. Stein PD, Henry JW, Relyea B. Untreated patients with pulmonary embolism: Outcome, clinical, and laboratory assessment. *Chest* 1995;107:931-935.
43. Laack TA, Goyal DG. Pulmonary embolism: An unsuspected killer. *Emerg Med Clin North Am* 2004;22:961-983.
44. Kim V, Spandorfer J. Epidemiology of venous thromboembolic disease. *Emerg Med Clin North Am* 2001;19:839-859.
45. Stein PD, Beemath A, Matta F, et al. Clinical characteristics of patients with acute pulmonary embolism: Data from PIOPED II. *Am J Med* 2007;120:871-879.
46. Sarasin FP, Louis-Simonet M, Carballo D, et al. Prospective evaluation of patients with syncope: A population-based study. *Am J Med* 2001;111:177-184.
47. Link MS, Lauer EP, Homoud MK, et al. Low yield of rule-out MI protocol in patients presenting with syncope. *Am J Cardiol* 2001;88:706-707.
48. Brignole M, Alboni P, Benditt DG, et al. Guidelines on the management (diagnosis and treatment) of syncope — update. *Eur Heart* 2004;25:2054-2072.
49. Chan TC, Vilke GM, Pollack M, et al. Electrocardiographic manifestations: pulmonary embolism. *J Emerg Med* 2001; 21:263-270.
50. Panos RJ, Barish RA, Whye DW Jr, et al. The electrocardiographic manifestations of pulmonary embolism. *Emerg Med* 1988;6:301-307.
51. Ullman E, Brady WJ, Perron AD, et al. Electrocardiographic manifestations of PE. *Am J Emerg Med* 2001;19:514-519.
52. Sreeram N, Cheriex EC, Smeets JLRM, et al. Value of the 12-lead EKG at hospital admission in the diagnosis of PE. *Am Cardiol* 1994;73:298-303.
53. Kosuge M, Kimura K, Ishikawa T, et al. Electrocardiographic differentiation between acute PE and ACS on the basis of negative T waves. *Am J Cardiol* 2007; 99:817-821.
54. Giannitsis E, Müller-Bardorff M, Kurowski V, et al. Independent prognostic value of cardiac troponin T in patients with confirmed pulmonary embolism. *Circulation* 2000;102:211-217.
55. Aksay E, Yanturali S, Kiyan S. Can elevated troponin I levels predict complicated clinical course and inhospital mortality in patients with acute pulmonary embolism? *J Emerg Med* 2007;25:138-143.
56. Mehta NJ, Jani K, Khan IA. Clinical usefulness and prognostic value of elevated cardiac troponin I levels in acute PE. *Am Heart J* 2003;145:821-825.
57. Stein PD, Fowler SE, Goodman LR, et al; PIOPED II Investigators. Multidetector computed tomography for acute pulmonary embolism. *N Engl J Med* 2006;354: 2317-2327.
58. Sadosty AT, Boie ET, Stead LG. Pulmonary embolism. *Emerg Med Clin North Am* 2003;21:363-384.
59. Bayes-Genis A, Mateo J, Santalo M, et al. D-dimer is an early diagnostic marker of coronary ischemia in patients with chest pain. *Am Heart J* 2000;140:379-384.
60. Shitrit D, Bar-Gil Shitrit A, Rudensky B, et al. Determinants of ELISA D-dimer sensitivity for unstable angina pectoris as defined by coronary catheterization. *Am J Hematol* 2004;76:121-125.
61. Antman EM, Braunwald E. ST-elevation myocardial infarction: Pathology, pathophysiology and clinical features. In: Libby P, Bonow RO, Mann DL, et al, eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 8th ed. Philadelphia, PA: Elsevier; 2008: 1207-1230.
62. Areskog M, Tibbling L, Wranne B. Oesophageal dysfunction in non-infarction coronary care unit patients. *Acta Med Scand* 1979;205:279-282.
63. Nebel OT, Frones MF, Castell DO. Symptomatic gastroesophageal reflux: Incidence and precipitating factors. *Am J Dig Dis* 1976;21:953-956.
64. Lowell MJ. Esophagus, stomach and duodenum. In: Marx, JA ed. R*osen's Emergency Medicine: Concepts and Clinical Practice*, 6th ed. St. Louis: Mosby; 2006: 1386-1398.
65. Pope JH, Selker HP. Acute coronary syndromes in the emergency department: Diagnostic characteristics, test, and challenges. *Cardiol Clin* 2005;23:423-451.
66. Clark LT, Adams-Campbell LL, Maw M, et al. Clinical features of patients with acute myocardial infarction presenting with and without typical chest pain: An inner city experience. *J Assoc Acad Minor Phys* 1989;1:29-31.
67. Pope J, Ruthazer R, Beshansky J, et al. Clinical features of emergency department patients presenting with symptoms of acute cardiac ischemia: A multicenter study. *J Thromb Thrombolysis* 1998;6:63-74.
68. Shry EA, Dacus J, Van De Graaff E, et al. Usefulness of the response to sublingual nitroglycerin as a predictor of ischemic chest pain in the emergency department. *Am J Cardiol* 2002;90:1264-1266.
69. Henrikson CA, Howell EE, Bush DE, et al. Chest pain relief with nitroglycerin does not predict active coronary artery disease. *Ann Intern Med* 2003;139:979-986.
70. Dobrzycki S, Baniukiewicz A, Korecki J, et al. Does gastro-esophageal reflux provoke myocardial ischemia in patients with CAD? *Int J Cardiol* 2005;104:67-72.
71. Swap CJ. Value and limitations of chest pain history in the evaluation of patients with suspected acute coronary syndromes. *JAMA* 2005;294:2623-2629.
72. Verdon F. Chest pain in daily practice: Occurrence, causes and management. *Swiss Med Wkly* 2008;138:340-347.
73. Lee TH, Cook EF, Weisberg M, et al. Acute chest pain in the emergency room: Identification and examination of low risk patients. *Arch Intern Med* 1985;145:65-69.
74. McElroy JB. Angina pectoris with coexisting musculoskeletal chest pain. *Am Heart J* 1963;66:96-99.
75. Panju AA, Hemmelgarn BR, Guyatt GH, et al. The rational clinical examination. Is this patient having a myocardial infarction? *JAMA* 1998;280:1256-1263.
76. Goldman L, Weinberg M, Weisberg M, et

al. A computer-derived protocol to aid in the diagnosis of emergency room patients with acute chest pain. *N Engl J Med* 1982;307:588-596.
77. Kessler RC, KA McGonagle, S Zhao, et al. Lifetime and twelve-month prevalence of DSM III-R psychiatric disorders in the United States: Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994;51:8-19.
78. Kercher EE. Anxiety. *Emerg Med Clin North Am* 1991;9:161-187.
79. Kanton WJ. Chest pain, cardiac disease and panic disorder. *J Clin Psychiatry* 1990; 51:27-30.
80. Jones ID, Slovis CM. Emergency department evaluation of the chest pain patient. *Emerg Med Clin North Am* 2001;19: 269-282.
81. Alonzo A, Simon A, Feilieb M. Prodromata of myocardial infarction and sudden death. *Circulation* 1975;52:1056-1062.
82. Canto JG, Shilpack MG, Rogers WJ, et al. Prevalence, clinical characteristics, and mortality among patients with myocardial infarction presenting without chest pain. *JAMA* 2000;283:3223-3229.
83. Kercher EE, Tobias JL. Anxiety disorders. In: Marx, JA ed. *Rosen's Emergency Medicine: Concepts and Clinical Practice*, 6th ed. St. Louis: Mosby; 2006: 1744-1752.
84. Nerenberg RH, Frances SS, Robey, et al. Impact of a negative prior stress test on emergency physician disposition decision in ED patients with chest pain syndromes. *Am J Emerg Med* 2007;25:39-44.
85. Shaver KJ, Marsan RJ, Sease KL, et al. Impact of a negative evaluation for underlying coronary artery disease on one-year resource utilization for patients admitted with potential acute coronary syndromes. *Acad Emerg Med* 2004;11:1272-1277.
86. Bruce RA. Exercise testing of patients with coronary artery disease. *Ann Clin Res* 1971;3:323-330.
87. Chaitman BR. Exercise stress testing. In: Libby P, Bonow RO, Mann DL, et al, eds. *Braunwald's Heard Disease: A Textbook of Cardiovascular Medicine*, 8th ed. Philadelphia, PA: Elsevier; 2008: 195-220.
88. Murthy TH, Bach DS. Comparative review of stress tests. *Clin Fam Pract* 2001;3: 801-816.
89. Gianrossi R, Detrano R, Mulvihill D, et al. Exercise-induced ST depression in the diagnosis of coronary artery disease: A meta-analysis. *Circulation* 1989;80:87-98.
90. Gibbons RJ, Chatterjee K, Daley J, et al. ACC/AHA/ACP-ASIM Guidelines for the Management of Patients with Chronic Stable Angina: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 1999;33:2092-2197.
91. Hachamovitch R, Berman DS, Kiat H, et al. Exercise myocardial perfusion SPECT in patients without known coronary artery disease: Incremental prognostic value and use in risk stratification. *Circulation* 1996;93:905-914.
92. Vanzetto G, Ormezzano O, Fagret D, et al. Long-term additive prognostic value of thallium-201 myocardial perfusion imaging over clinical and exercise stress test in low to intermediate risk patients: Study in 1137 patients with 6-year follow-up. *Circulation* 1999;100:1521-1527.
93. Udelson JE, Dilsizian V, Bonow RO. Nuclear cardiology. In: Libby P, Bonow RO, Mann DL, et al, eds. *Braunwald's Heard Disease: A Textbook of Cardiovascular Medicine,* 8th ed. Philadelphia, PA: Elsevier; 2008: 345-389.
94. Thom T, Haase N, Rosamond W, et al. Heart disease and stroke statistics-2006 update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2006;113:e85-e151.
95. Morrow DA, Gershe BJ. Chronic coronary artery disease. In: Libby P, Bonow RO, Mann DL, et al, eds. *Braunwald's Heard Disease: A Textbook of Cardiovascular Medicine*, 8th ed. Philadelphia, PA: Elsevier; 2008: 1353-1405.
96. Califf RM, Armstrong PW, Carver JR, et al. Task Force 5: Stratification of patients into high-, medium-, and low-risk subgroups for purposes of risk factor management. *J Am Coll Cardiol* 1996;27:1007-1019.
97. Cohnn PF. Prognosis and treatment of asymptomatic coronary artery disease. *J Am Coll Cardiol* 1983;1:959-964.
98. Libby P, Theroux P. Pathophysiology of coronary artery disease. *Circulation* 2005;111:3481-3488.
99. Serruys PW, Kutryk MJB, Ong ATL. Coronary-artery stents. *N Engl J Med* 2006;354:483-495.
100. Cutlip D, Chauhan M, Baim D, et al. Clinical restenosis after coronary stenting: Perspectives from multicenter clinical trials. *J Am Coll Cardiol* 2002;40:2082-2089.
101. Popma JJ, Tulli M. Drug-eluting stents. *Cardiol Clin* 2006;24:217-231.
102. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;293: 2126-2130.
103. Heublein B, Rohde R, Kaese V, et al. Biocorrosion of magnesium alloys: A new principle in cardiovascular implant technology? *Heart* 2003;89:651-656.
104. Serruys PW, Ong ATL, Morice M-C, et al. Arterial Revascularisation Therapies Study. II. Sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. *Eurointervention* 2005;1:147-156.
105. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004;364:1519-1521.
106. Prinzmetal M, Kennamer R, Merliss R, et al. A variant form of angina pectoris. *Am J Med* 1959;27:375-388.
107. Cannon CP, Braunwald E. Unstable angina and non-ST elevation myocardial infarction. In: Libby P, Bonow RO, Mann DL, et al, eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 8th ed. Philadelphia, PA: Elsevier; 2008: 1319-1340.
108. Burnsides C, Edwards JC, Lansing AI, et al. Arteriosclerosis in the intramural and extramural portions of coronary arteries in the human heart. *Circulation* 1956;13: 235-241.
109. Tsujita K, Maehara A, Mintz GS, et al. Comparison of angiographic and intravascular ultrasonic detection of myocardial bridging of the LAD coronary artery. *Am J Cardiol* 2008;102:1608-1613.
110. Pepine CJ, Balaban RS, Bonow RO, et al. Women's Ischemic Syndrome Evaluation: Current status and future research directions: Report of the National Heart, Lung and Blood Institute workshop: October 2-4, 2002: Section 1: Diagnosis of stable ischemia and ischemic heart disease. *Circulation* 2004;109:e44-e46.
111. Bugiardini R, Bairey Merz CN. Angina with "normal" coronary arteries: A changing philosophy. *JAMA* 2005;293:477-484.
112. Kemp HG, Kronmal RA, Vlietstra RE, et al. Seven year survival of patients with normal or near normal coronary ateriograms: A CASS registry study. *Am Coll Cardiol* 1986;7:479-483.
113. Panting JR, Gatehouse PD, Guang-Zhong Y, et al. Abnormal subendocardial perfusion

in cardiac syndrome X detected by cardiovascular MRI. *N Engl J Med* 2002;346: 1948-1953.
114. Suwaidi JA, Hamasaki S, Higano ST, et al. A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. *Circulation* 2000;101: 948-954.

Physician CME Questions

111. The percentage of clinically silent PE in patients with a diagnosis of DVT is:

A. < 10%
B. 10-20%
C. 20-30%
D. 30-40%
E. 40-50%

112. ECG findings suggestive of ischemia are seen in what percentage of patients with acute aortic dissection?
A. < 10%
B. 10-20%
C. 20-30%
D. 30-40%
E. 40-50%

113. Troponin levels are elevated in what percentage of patients with PE?
A. 95%
B. more than 70%
C. up to 80%
D. up to 45%

114. Relief of chest pain with:
A. antacids is not seen in patients with acute MI
B. nitroglycerin is seen in a majority of patients with non-cardiac chest pain
C. nitroglycerin proves pain is from cardiac ischemia
D. none of the above

115. Screening of chest pain patients with exercise testing/perfusion studies:
A. is most helpful in patients with low risk of cardiac disease
B. is most helpful in patients with intermediate risk of cardiac disease
C. is most helpful in patients with high risk of cardiac disease
D. makes no difference

116. False-negative exercise perfusion scans:
A. can occur in patients with left main disease
B. can occur in patients with proximal triple-vessel disease
C. are seen in 10% of patients
D. all of the above

117. According to cardiology texts, a negative perfusion scan can predict a low incidence (< 0.4%) of MI or death for up to:
A. 2 months
B. 6 months
C. 12 months
D. 18 months
E. 24 months

118. Which of the following statements concerning patients with recent cardiac catheterization is *false*?
A. They are at high risk of MI when aspirin and clopidogrel are stopped after drug-eluting stent placement
B. Results should be verified when the patient reports the procedure as "normal."
C. A truly negative catheterization in past 6 months rules out presence of acute MI.
D. Negative catheterization results are more common in women than men.

119. Known mechanisms of acute MI in patients with recent negative catheterization results include:

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.

A. bridging of coronary vessels (systolic compression of vessel by surrounding muscle)
B. coronary spasm
C. vessel lesion was extra-lumenal
D. diffuse subendocardial ischemia of thick ventricle wall
E. all of the above

120. What features are commonly used to distinguish chest wall pain from myocardial ischemia?
A. Reproducibility with palpation
B. Variation with respiration
C. Both A and B
D. Neither A or B1

CME Answer Key

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

In Future Issues
Near Drowning

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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.

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Emergency Medicine Reports
The Practical Journal for Emergency Physicians

Misdiagnoses of Myocardial Infarction

Avoid Misdiagnosing Acute Aortic Dissection as Acute MI

High Risk Clinical Features:

- Sudden onset and/or tearing/ripping pain
  - Sudden onset in 85%
  - Only 50% describe as tearing/ripping
- Widened mediastinum on chest radiograph
  - Only 61% of patients have widened mediastinum
  - 12% of films are normal
- Pulse/blood pressure differences
  - 15–30% have pulse deficits
- Presence of all 3 findings seen in 83% of acute dissections
- Absence of all 3 seen in only 7% of acute dissections

Know the Risk Factors:

- History of hypertension
- Age > 60 years
- Male more often than female (68% vs 32%)
- For patients < 40 years old:
  - Marfan's syndrome
  - Ehlers-Danlos syndrome
  - Pregnancy (third trimester)
  - Bicuspid aortic valve
  - Cocaine — recent use

Tests Can Suggest Acute Cardiac Ischemia

- ECG:
  - 31% of ECGs are normal
  - Up to 26% will have ECG findings suggestive of AMI or ischemia
  - 22% of ECGs have non-STEMI changes
  - 4% have STEMI changes
- Troponin:
  - Up to 23% can have elevated troponin I

Diagnosis

- No reliable serum marker has yet been identified
- D-dimer levels > 400 ng/mL are seen in most dissections
- BUT it is not specific enough to rule out dissection if absent
- Chest CT, TEE, angiography, or MRI remain the definitive modalities for diagnosis

Avoid Misdiagnosing Acute Pulmonary Embolism as Acute MI

High Risk Clinical Features:

- Sudden-onset of dyspnea combined with syncope
  - However, 50% do not have sudden onset
- Elderly patient
  - PE seen 10 times more often in those > 75 years of age
- History of PE risk factors
  - Recent surgery
  - Immobility
  - Obesity
  - Cancer
  - COPD
  - CHF
  - Previous MI

Tests Can Suggest Acute Cardiac Ischemia

- ECG:
  - 27% of ECGs are normal in PE
  - T wave inversions in leads III and V1 are associated with PE rather than myocardial ischemia
  - Remember ECG findings of S1Q3T3 and RBBB may be transient
- Troponin:
  - Up to 45% can have elevated troponin I (< 4–5 ng/dL)
  - Is a marker of right heart strain

Diagnosis

- Negative D-dimer levels rule out PE in LOW risk patients only
- Beware of negative chest CT for PE when patient is high risk
  - PIOPED II suggests VQ scan to confirm
- Treatment is effective
  - Mortality reduced from 25% to 5%

Common Misdiagnoses for Acute MI

GERD

- Often described as a "squeezing" chest pain
- Associated symptoms of diaphoresis, nausea, vomiting also common
- Can radiate to neck, jaws, shoulders, back and arms
- Risk factors: diabetes, tobacco use, obesity
- Nitroglycerin commonly relieves reflux pain
  - Antacids also can relieve pain of acute MI
- Useful identifying features of GERD
  - Acid refluxing into mouth
  - Water brash (brief hypersalivation)
  - Symptoms are positional — worse bending and lying down
  - Often triggered by large, spicy meals
  - Tend to be chronic in nature (occurring for years)

Musculoskeletal Chest Pain

- Pleuritic pain lowers risk of acute MI, but does not rule it out
  - Seen in 13–15% of acute MI patients
- Pain reproduced by palpation lowers risk, does not rule out MI alone
  - Seen in 7–15% of acute MI patients
- History of PE risk factors
  - Recent surgery
  - Immobility

Anxiety

- Can present with acute chest pain, SOB, palpitations
- Beware as dyspnea can be the chief complaint in acute MI
  - 13–33% of acute MI patients present with dyspnea
  - Dyspnea is the number one complaint in elderly patients with MI

Exercise Testing and Perfusion Studies

Contraindications

- Absolute
  - Unstable angina
  - Evolving ECG changes
  - Abnormal cardiac biomarkers
  - Significant CHF
  - Significant aortic stenosis
  - Severe hypertension (> 200 mmHg systolic, > 110 mmHg diastolic)
  - Clinical indication that coronary angiography is needed
- Relative
  - Valvular heart disease, anemia
  - Interventricular conduction delays (including bundle branch blocks)
  - Hypokalemia
  - Hypoxia or volume overload
  - Beta blocker use

Limits of Utility

- Exercise test
  - Baseline ECG changes make interpretation difficult
  - False positive results common in patients with relative contraindications
  - Most useful for patients with intermediate risk of disease
- Perfusion study
  - Can miss global ischemia (left main, 3-vessel disease)
  - Microvascular disease can simulate large vessel disease

Prognostic Value

- Sensitivity/specificity
  - 68% and 77% for exercise stress
  - 90% and 70% for perfusion
  - Numbers for both tests are in terms of ability to detect coronary lesions with > 50% obstruction
- Negative tests do NOT mean absence of coronary disease, but do help predict patients at risk for near-term cardiac events (MI/death)
- Perfusion study numbers hold up for 2 years into future
  - Normal study = 0.4% risk of MI/death per year
  - Multiple abnormal segments = 9% risk of MI/death per year

The Patient with Recent Cardiac Catheterization (< 6-12 months)

Recent Stent Placement

- Patients must stay on aspirin/clopidogrel (Plavix) for 6–12 months or longer after placement of drug-eluting stent
  - High risk of re-stenosis and STEMI if non-compliant
  - Currently recommended to stay on aspirin therapy for life
- Diabetics have twice the risk of re-stenosis compared to non-diabetics

Recent Negative Catheterization

- Verify results when patients report them as “negative”
  - Truly negative = no evidence of disease
  - Patient may only mean no intervention was required
- Patients with negative catheterization still can have acute MI
  - Coronary spasm (Prinzmetal angina, cocaine)
  - Bridging vessels — dive into muscle instead of staying on surface and are compressed in systole
  - Microvascular disease
  - Subendocardial ischemia with severe LVH
- Negative catheterization does not rule out all coronary disease, but patient is at lower risk than those not yet studied
  - 96% survival rate for 7 years with negative catheterization
  - 92% survival rate for 7 years with mild lesions (<50%)
- Patient with “good story” for angina and multiple risk factors should still be evaluated for possible AMI or USA
  - Cath = lumenogram
  - Can have extralumenal coronary lesions which can still produce AMI

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Fluid Management in Adult and Pediatric Trauma Patients

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Peer Reviewer: **Dennis Hanlon, MD, FAAEM**, Vice Chairman, Academics, Department of Emergency Medicine, Allegheny General Hospital, Pittsburgh, PA.

Fluid therapy is an integral aspect of trauma resuscitation. With advances in resuscitation research, controversies abound regarding approaches to the initial fluid management. Advanced Trauma Life Support (ATLS) guidelines recommend an initial rapid infusion of fluid (1–2 liters) in trauma and hemorrhage victims as a diagnostic procedure to aid treatment decisions.[1] To determine therapeutic strategies, patients' response to the initial fluid challenge is very important. However, the appropriate rate of infusion and the choice of fluid have not been clearly defined.[1] The ATLS program by the American College of Surgeons provides a chart that allows monitoring of patients' response to the initial fluid resuscitation.[2] (See Table 1.)

Controversies also abound about pre-hospital fluid therapy in patients with blunt and penetrating injuries, as well as pediatric and head injury patients. It is often difficult to draw conclusions from the available body of literature because of the significant variation in study designs, target hemodynamic parameters, the type of population utilized, and the end point of resuscitation. Furthermore, consensus studies that utilize meta analysis are hard to interpret because of the extreme variation in the collected data and the inclusion of very old data. This article will not propagate the controversies, but rather extensively review pertinent literature from the last decade (1998–2008), with the goal of providing some clarification to these controversies.

— The Editor

Choice of Fluid

A discussion of fluid management would be incomplete without a detailed review of the fluids available for resuscitation. The ideal resuscitation fluid should be capable of carrying oxygen, have little or no effect on coagulation, be inexpensive and non-allergic or antigenic, and possess a relatively long shelf life at room temperature. At present, none of the available fluids have all

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these qualities. Currently available fluids for resuscitation include crystalloids, colloids, and blood products.

Crystalloids. Crystalloids are water solutions of inorganic ions and small organic molecules. They have increased volume of distribution that encompasses the entire interstitial and intercellular compartment. Owing to capillary permeability, they have limited half-life because they easily escape from the intravascular space into the tissues.[3,4] When crystalloids are infused, about 75% extravasate into the interstitial space, while only 25% remain in the intravascular space.[4]

Based on pharmacokinetics, the general rule is that three volumes of crystalloids replace one volume of lost blood. This rule originated from the study done by Shires and colleagues in the 1960s that demonstrated that about three times the volume of blood loss of isotonic crystalloid is required to restore extra-cellular deficit during hemorrhagic shock.[5] Crystalloid-based resuscitation has mainly dosage-related side effects, which include fluid overload, albumin dilution, reduction of plasma oncotic pressure, and tissue edema. Commonly utilized crystalloids are isotonic (normal saline and lactated Ringer's [LR]), hypertonic (3%, 6%, and 7.5% NaCl) saline (HTS), and hypotonic (D5 water) solution.

Normal saline solution is a mildly hypertonic crystalloid with increased sodium and chloride concentration when compared to plasma. The solution is a suitable blood dilutent, since it does not contain calcium that could potentially interact with the citrate component in blood. In resuscitation, large volumes of normal saline are often required to obtain similar hemodynamic effects when compared to HTS. This increased volume potentially increases transvascular filtration of fluids and protein, increased interstitial fluid, increased capillary permeability, and increased pulmonary artery pressure, with subsequent development of pulmonary edema. The utilization of normal saline in the large volumes required in hemorrhaging patients could lead to hyperchloremic metabolic acidosis. This non-anion gap acidosis could potentially interfere with acid–base interpretation. Base deficit is one of the parameters utilized in guiding adequacy of resuscitation; the hyperchloremia produced by large volumes of normal saline may lead to persistent base deficit. A study by Skellet and colleagues concluded that "normal saline (0.9% saline) and other chloride-rich fluids may not be ideal resuscitation fluids; if used, clinicians must be aware of their potential to cause persistent base deficit." Normal saline is not currently the initially recommended resuscitation fluid, according to ATLS guidelines.[6]

ATLS guidelines recommend LR solution as the recommended initial resuscitation fluid. However, several recent studies have shown deleterious effects of this solution. The complication seen in trauma resuscitation has been attributed to the activation of the inflammatory system cascade and the type of fluid utilized. LR, in particular, has being implicated in this hyper-inflammatory state.[4,7,8] Rhee and colleagues demonstrated that neutrophil activation increased significantly after hemorrhage, but the rise was greatest with LR resuscitation.[9] They also inferred that neutrophil activation may be caused by LR and not reperfusion. Other studies demonstrated significant neutrophil activation with LR solution, and have also shown that resuscitation with LR solution leads to greater hypercoagulability when compared to normal saline.[10,11]

The currently utilized LR solution is a racemic mixture of the L and D isomers. The deleterious effect seen with LR resuscitation has been shown to be attributed to the D-isomer. Kaustova and colleagues studied the effects of LR solution on human leukocytes.[12] Using donated blood from human volunteers, they were able to show that when compared with the L-LR isomer, the D-LR isomer causes an increased expression in genes responsible for inflammation, neutrophil activation, and cell migration.

The initial changes the endothelium undergoes to modulate inflammation in response to trauma and hemorrhagic shock could also be exacerbated by the choice of resuscitation fluid. Savage and colleagues performed a study to evaluate the effect of LR solution on endothelial function during resuscitation for hemorrhagic shock.[13] The study showed that resuscitation with LR requires larger volume, and also causes a decrease in endothelial dependent relaxation (EDR), leading to endothelial dysfunction.

Jaskille and colleagues performed a study to determine if the elimination of D-Lactate isomer will attenuate liver apoptosis.[14] Rats in a controlled hemorrhage model were stratified to receive different resuscitation fluid, including racemic (D and L) mixture and solution containing only the L-lactate isomer. The result shows that racemic LR solution induces liver apoptosis, which is decreased if the D-isomer was eliminated. A study using a swine model also demonstrated that clearance of lactic acid was impeded following resuscitation with the DL racemic mixture.[15] However, this was not seen in the L-isomer solution. Hence, elimination

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Table 1. Responses to Initial Fluid Resuscitation

	RAPID RESPONSE	TRANSIENT RESPONSE	NO RESPONSE
Vital signs	Return to normal	Transient improvement, recurrence of lowered BP, and increased HR	Remain abnormal
Estimated blood loss	Minimal (10-20%)	Moderate and ongoing (20-40%)	Severe (>40%)
Need for more crystalloid	Low	High	High
Need for blood	Low	Moderate to high	Immediate
Blood preparation	Type and cross-match	Type-specific	Emergency blood release
Need for operative intervention	Possibly	Likely	Highly likely
Early presence of surgeon	Yes	Yes	Yes

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of the D-isomer from the conventional racemic mixture will eliminate the deleterious effect attributed to LR resuscitation.

HTS has been used successfully in both animals and human models of hemorrhagic shock. The typical 7.5% HTS has osmolality of 2400 Mosml/L. It requires a smaller volume of about 4–5 mL/kg to effectively restore cardiovascular function.[4,5,8] Several characteristics of HTS make the solution promising for resuscitation. It has a direct vasodilatory effect in the systemic and pulmonary circulation, thus reducing venous capacitance. These effects result in the increase in mean arterial pressure (MAP), cardiac output (CO), and renal, mesenteric, total splanchnic, and coronary blood flow.[7]

Furthermore, HTS has been shown both in vivo and in vitro to display some immune modulating effects such as inflammatory mediation, neutrophil down-regulation, and macrophage activation.[4,8] Studies have shown that HTS resuscitation after hemorrhagic shock prevents the development of lung injury when compared to LR, which shows significant lung derangement.[16] This finding was attributed to the ability of HTS to reduce neutrophil oxidative burst and lung neutrophil influx. These inherent characteristics of HTS are transient. However, this could be extended by mixing HTS with colloids. A currently utilized mixed solution is HTS-Dextran (typically NaCl 7.5% + Dextran-70, 6%).[17]

Several studies have shown that low-dose HTS dextran reduces the risk of lethal rebleeding in uncontrolled hemorrhage, and demonstrated that HTS results in rapid restoration of hemodynamics with laboratory evidence of improved microcirculatory hemodynamics.[17,18] Another study, which utilized the small volume concept of HTS/hydroxyethyl starch (HES) solutions, showed reduced blood loss and less impairment of hemostasis in pigs after resuscitation from hemorrhagic shock.[19]

In combat casualties, HTS is routinely utilized with great results. According to the recommendation for the initial fluid resuscitation in combat casualties, if vital signs and mental status are normal, intravenous access should be established but fluid withheld. However, if vital signs and mental status are abnormal, intravenous access should be established and 7.5% HTS given, up to 500 mL. If more fluid is needed, the recommendation was to switch to colloids or isotonic saline.[20]

Colloids are heterogeneous resuscitation fluids with increased molecular size and weight. They have similar volume of distribution as the crystalloids, which are limited to the intravascular space. They are often referred to as volume expanders because of their inherent characteristic variable molecular size and water-retaining capability. Agents in this category also have side effect profiles that are dose-related, and potential anaphylactic reactions.[3,4,8] Commonly available colloids include albumin, dextran, gelatin, and HES.

Albumin, which is synthesized in the liver, is the prototype colloid. Its molecular weight (69 kd) determines plasma oncotic pressure. An extensive review performed by the Cochrane group in 1998 on 37 randomized controlled trials comparing albumin with crystalloids concluded that the odds ratio of mortality was significantly increased in patients given albumin.[21] However, these results have not been reproducible.[22,23] The SAFE study, which was an attempt to challenge the validity of the Cochrane report, enrolled 7,000 patients from 2000 to 2002, with end point of 28 days all-cause mortality in critically ill patients receiving 4% albumin or saline. Their findings did not support the Cochrane report, and they concluded that "albumin is SAFE." Presently, albumin is not frequently utilized as a volume expander in resuscitation because of cost and other options.

Dextran is a glucose polymer available in two different molecular weights (70 kd and 40 kd) and has been extensively used as a volume expander. Its utility has been limited due to harmful side effects, which include severe hypersensitivity reactions and coagulation abnormalities.[24,25]

Gelatins are derived from bovine collagen, and have very low molecular weight (35–40 kd). Owing to molecular size and relatively short half-life, they are not an effective volume expander, though they have less hypersensitivity reaction when compared to dextrans.[24,25]

HES are the most commonly used colloids. They are derived from amylopectin extracted from maize and conjugated with eth-

Table 2. Summary of Recent Polyheme Studies

Study	Number of patients	Indication for Polyheme	Results
Gould et al, 1997	39	Received up to 6 units of Polyheme in lieu of RBC	Polyheme maintained total Hb in lieu of RBC in acute blood loss
Gould et al, 1998	44	Randomized to receive RBC or up to 6 units Polyheme as initial resuscitation	Amount of RBC given on day 1 was significantly less for Polyheme group
Johnson et al, 1998	13	Randomized to receive RBC or up to 6 units Polyheme as initial resuscitation	Polyhemes lack the vasoconstrictive effects associated with other HB-based substitutes
Gould et al, 2002	171	Compared patients who were given up to 20 units of Polyheme with historical patient who refused blood	Polyheme increased survival at life-threatening HB levels by maintaining total HB without RBC transfusion
Johnson et al, 2003	25	Compared rates of multiple organ failure in patients receiving Polyheme and those receiving RBC	Relative increase in post-inflammatory cytokines as well as counter-regulatory cytokines was less with Polyheme

Source: Polyheme, Northfield Laboratories Inc., Evanston, IL.

ylene oxide. Amongst all HES, pentastarch has the most anti-inflammatory effect and efficiently retains more fluid in the intravascular space. All HES have side effect profiles similar to dextrans (anaphylaxis and coagulation abnormalities).[3] A study that evaluated the beneficial effects of HES in a near-fatal model of hemorrhagic shock demonstrated that early colloid infusion with modern HES solution resulted in prompt recovery of tissue perfusion when compared with the infusion of equal volume of LR solution.[26]

Hemoglobin-based oxygen carriers (HBOC) are hemoglobin-based products referred to as oxygen therapeutics. These are compounds derived from outdated human packed red blood cells or bovine red blood cells through a process of lysis and filtration.[18] Owing to their characteristic high oxygen-carrying capacity at ambient partial pressure, they can either augment or replace the oxygen-carrying capacity of red blood cells (RBCs).

The HBOCs have been tested in multiple settings to temporarily augment oxygen-carrying capacity without utilizing RBC transfusion in situations such as trauma resuscitation, resuscitation during surgery involving large blood loss, and intraoperative autologous blood donation during cardiac surgery.[27] Available data have shown that when used during active hemorrhage, HBOCs can temporarily maintain adequate oxygen-carrying capacity and intravascular volume until hemorrhage is controlled. When utilized in this fashion, HBOCs minimize exposure to banked blood, and therefore decrease potential for exposure to infectious agents and the negative immunologic effects associated with banked blood.

A study by Moore and colleagues shows that transfusion of more than six units of packed RBC during the initial resuscitation of trauma patients is an independent predictor of multiple organ failure.[28] This effect was theorized to be due to the pro-inflammatory effect of substances present in banked blood. It could be extrapolated from this study that reducing exposure to banked blood during trauma resuscitation should improve outcome.

Another study evaluated the utility of HBOC solution in the resuscitation of patients with severe chest trauma.[29] Using an anesthetized swine model and four different types of HBOC solutions, the authors found that all HBOCs were pressors and all reduced the supplemental fluid required to maintain systemic hemodynamics during resuscitation. However, the pressor characteristics also increased right and left ventricular afterload that further compromised marginal cardiac performance.

As a new therapeutic modality, concerns about HBOC's potential side effects abound. Some of the concerns are nephrotoxicity, vasoconstriction, methemoglobinemia, and neurotoxic effect on the brain. Although nephrotoxicity has been almost completely eliminated with the polymerization of the components, the vasoconstriction still persists. The methemoglobinemia is, however, dose-dependent.

Overall, HBOC may be the future of RBC-free resuscitation. The currently available HBOC preparations in the United States are Polyheme (Northfield Labs), Hemopure (Biopure Inc.), and Hemolinks (Hemosol Inc.). All these products are currently in phase III trials. Polyheme is so far the only HBOC with trials in human trauma subjects, and it's showing significant promise.[30-35] *(See Table 2.)*

After review of the available resuscitation fluids, and knowing the components and the adverse effect profiles, crystalloids should be the initial fluid of choice in trauma patients in the absence of contraindication, since they lack the adverse effects seen in other resuscitation fluids. However, studies are showing the benefits of HTS in low-volume resuscitation for traumatic brain injury (TBI), hemorrhagic shock, and also as the initial fluid

for resuscitation of hypotensive trauma patients. Presently, utilization of HTS is not approved by the U.S. Food and Drug Administration (FDA), though it is currently utilized in Europe and in the military.

Pre-Hospital Resuscitation

The importance of the emergency response teams to trauma victims cannot be overstated. Fluid administration in the pre-hospital setting is a challenging and controversial area. Despite advances in research, there is no unequivocal view that can be supported by well documented and reliable evidence. However, several consensus data that culminate the review of available body of evidence over the past decade are beginning to streamline parameters to guide pre-hospital personnel regarding approach to a trauma victim.

Table 3. Classes of Shock

	CLASS I	CLASS II	CLASS III	CLASS IV
Blood loss (mL)	Up to 750	750–1,500	1,500–2,000	>2,000
Blood loss (% blood volume)	Up to 15%	15%–30%	30%–40%	>40%
Pulse rate (bpm)	<100	>100	>120	>140
Blood pressure	Normal or increased	Decreased	Decreased	Decreased
Respiratory rate	14–20	20–30	30–40	>40
Urine output (mL/hr)	>30	20–30	5–15	Negligible
CNS/mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic
Fluid replacement (3:1 rule)	Crystalloid	Crystalloid	Crystalloid and blood	Crystalloid and blood

Used with permission from: American College of Surgeons Committee on Trauma. Advanced Trauma Life Support for Doctors: Student Course Manual, 8th edition. Chicago,IL: American College of Surgeons; 2008:61.

The principle of advanced life support for paramedics traditionally involves early, rapid intravenous fluid replacement to increase circulating volume and blood pressure with the belief that this will maintain vital organ perfusion, thereby improving outcome and survival.[2] Currently, the available data may demonstrate that many longstanding practices for pre-hospital fluid resuscitation may be detrimental. The prevailing question now is how do pre-hospital personnel perform fluid resuscitation? The debate between under-resuscitation versus over-resuscitation has been raging over several decades. A study by Riddez and colleagues attempted to answer this question.[36] Standardized aortotomy was performed in dogs stratified into four resuscitation groups — no fluid, 1:1 LR, 2:1 LR, and 3:1 LR volume ratio. The study showed that the rate of bleeding and aortic blood flow increased with amount of fluid used. Also, the highest mortality was seen in the no-fluid and the 3:1 LR resuscitation groups. These findings were attributed to shock in the no-fluid group and re-bleeding in the aggressively resuscitated group.

To streamline pre-hospital personnel's approach to fluid resuscitation, there have to be set diagnostic parameters that rapidly identify hypoperfusing , hypotensive, or potentially unstable trauma patients. Currently available parameters utilized, such as heart rate, blood pressure, and cyanosis, are often influenced by the effects of drugs and alcohol, pain, pneumothorax, and spinal cord injury. Such multifactoral influences render these markers potentially unreliable as guides to therapeutic goals.[37,38]

The approach to trauma patients in the pre-hospital setting should involve a strategy that employs immediate stratification by mechanism of injury (blunt vs. penetrating), anatomic involvement (truncal vs. isolated head or extremity injuries), and condition staging (hemodynamically stable vs. unstable or moribund), and also an understanding of the different classes of shocks as described in ATLS guidelines.[39] *(See Table 3.)*

Using this approach, most of the controversies that surround pre-hospital fluid resuscitation could be resolved. Based on available data, liberal use of fluid in presumed uncontrolled bleeding in a penetrating trauma patient is no longer advised.[40-42] The priority of paramedics in this situation is localized control of obvious hemorrhage, rapid evacuation, and intravenous cannulation en route to definitive surgical intervention.[42,43]

Extensive review shows that when it comes to fluid resuscitation in the pre-hospital setting, most consensus data seem to arrive at the same conclusion. The current recommendations for fluid resuscitation in the United Kingdom, the Joint Royal Colleges Ambulance Liaison Committee (JRCALC) guidelines (2004), state that "intravenous infusion should be commenced en route to the hospital, and only sufficient fluid given to maintain systolic blood pressure of 80–90 mmHg."[42] They recommend that "500 mL IV of crystalloid solution should be given, and the effects on the circulatory system be assessed before further fluid is given."[42]

Berlot and colleagues reported in 2006 that "in the presence of a disturbance of consciousness, it is safer to obtain a relatively elevated systolic arterial pressure of 120–130 mmHg to prevent the occurrence of secondary brain injury, whereas lower values of systolic arterial pressure of 90 mmHg are tolerated in trauma patients without any neurologic injury provided arrival at the hospital does not exceed 30–40 minutes."[44]

In blunt trauma patients, the resuscitation modality is the same. In a paired case-control study on a blunt trauma patient with scene systolic blood pressure less than or equal to 90 mmHg, one arm received more than 500 mL of fluid and the other arm

received no fluid. The study concluded that pre-hospital fluid resuscitation of blunt-injured trauma patients with systolic blood pressure less than or equal to 90 mmHg increases systolic blood pressure but has no effect on survival or length of hospital stay.[43] Another group summarized that the goal in blunt injury is to secure safe perfusion of the injured brain through adequate cerebral perfusion pressure (SBP > 100 mmHg); patients without brain injury tolerate lower blood pressure.[45] They also recommended that the ideal pre-hospital fluid regimen may be a combination of an initial hypertonic solution given as an infusion over 10–20 minutes, followed by crystalloids.[45]

According to a consensus view by Revell and colleagues, fluid should not be administered to trauma patients in the pre-hospital setting before hemorrhage control if a radial pulse can be palpated.[46] Judicious fluid of 250 mL should be titrated for other patients. If the radial pulse returns, fluid resuscitation can be suspended and the situation monitored. *(See Table 4.)*

ED-based Resuscitation

The arrival of a trauma patient in the hospital begins the phase of definitive care. The goal of this phase is to control hemorrhage, ensure adequate end organ perfusion, increase oxygen delivery to tissues, normalize base deficit, obtain a perfusing blood pressure, and prevent reperfusion injury.The mantra that has been propagated over the years is to obtain two large-bore vascular accesses and infuse 1–2 liters of saline to return blood pressure to pre-injury level. Several recent experimental studies have discouraged this approach.

Presently, the trend in the field of resuscitation is to restrict the amount of fluid utilized. This is based on the theory that aggressive intravenous fluid resuscitation in a hemorrhaging patient may actually promote increased bleeding. The increase in blood pressure to near normal in a hypotensive trauma patient may dislodge hemostatic clots, alter blood viscosities, and cause hemodilution of platelets and clotting factors.[47]

Restrictive or low-volume resuscitation is not a new phenomenon. In 1918, Cannon pointed out the disadvantages of fluid resuscitation and emphasized that an increase in blood pressure before surgical hemostasis would "pop the clot" and increase bleeding with potential exsanguination.[48] Cannon also warned that "injection of a fluid that will increase blood pressure has danger in itself. Hemorrhage in case of shock may not have occurred to a marked degree because pressure has been too low to overcome the obstacle offered by a clot. If pressure is raised before checking the bleeding, blood that is sorely needed may be lost."

The term "permissive hypotension" is the current trend in trauma resuscitation. Despite favorable evidence and increasing proponents of this modality, opponents still contend with the idea of hypotensive resuscitation. Opponents raise the concerns of the consequences of avoidance of fluid in the early phases of hypotensive trauma patient resuscitation. The contention was that hypotensive resuscitation leads to hypoperfusion, organ failure, death prior to bleeding control, and deleterious effect on patients with concomitant head injury. Despite these contentions, there are overwhelming data to support restrictive fluid resuscitation or permissive hypotension in the treatment of a patient with uncontrolled hemorrhaging until definitive surgical intervention is available. However, there are special considerations for head-injured patients.

A randomized control study on human subjects presenting in hemorrhagic shock and stratified into two fluid treatment arms concluded that titration of initial fluid therapy to a lower-than-normal systolic blood pressure during active hemorrhage did not affect mortality.[49] Another study performed on sheep that underwent left anterior thoracotomy with transection of the left internal mammary artery suggested that early, aggressive fluid resuscitation in penetrating thoracic trauma exacerbated total hemorrhage volume.[50]

Krausz and colleagues, using the standard massive spleen injury (MSI) model of uncontrolled hemorrhage, studied the effect of vigorous crystalloid or colloid fluid resuscitation on hemodynamic response and survival in rats.[51] The study revealed that vigorous large-volume infusion of LR solution or HES following MSI resulted in a significant increase in intra-abdominal bleeding and shortened survival time when compared with those untreated and those treated with small-volume HTS and HES-7.5% solutions.

A group using the standardized MSI model of uncontrolled hemorrhagic shock evaluated the effects of continuous fluid resuscitation and splenectomy on the hemodynamic response and survival in rats. Their study showed that continuous infusion of large-volume LR with splenectomy after MSI resulted in significant increases in intra-abdominal bleeding and shortened survival time compared with small-volume LR infusion.[52]

In a study evaluating the general and pathophysiologic effects of controlled fluid resuscitation in the treatment of severe and uncontrolled hemorrhagic shock, rat models were stratified into no fluid, controlled fluid, and aggressive fluid resuscitation arms.[51] The study concluded that "among the three resuscitation arms, controlled fluid resuscitation can effectively decrease additional blood loss, minimize hemodilution and coagulopathy, improve early survival rate, and reduce apoptosis of visceral organs in rats with severe and uncontrolled hemorrhagic shock."[53]

With strong evidence to support small-volume resuscitation, this modality should be embraced as the standard of care when resuscitating hypotensive, hemorrhaging trauma patients. However, this standard should exclude patients with TBI, since hypotension has been shown to promote secondary brain injury. The discussion that follows will elaborate on the care of patients with TBI.

Traumatic Brain Injury Considerations

TBI is the leading cause of trauma-related mortality. Despite advances in current treatment strategies, the overall mortality still ranges from 31% to 49%.[54] Among the survivors, large proportions have persistent severe neurologic disability, with the estimated lifetime cost for each individual exceeding $2 million.[55]

Preventable morbidity and mortality following the initial head trauma is a consequence of the secondary brain injury that occurs due to hypoxia, hypotension, and elevated intracranial pressure (ICP).

The deleterious effect of hypotension in TBI has been well documented. Studies have shown that patients with hypotension after severe TBI have twice the mortality of normotensive patients.[56] Consequently, aggressive resuscitation with intravenous fluid is recommended in the current guidelines for management of severe TBI.[57] The question that arises now is, How aggressively should we resuscitate in the era of permissive hypotension?

The primary therapeutic goal in a non-operative TBI patient should be to maintain adequate mean arterial pressure (MAP), control ICP, and provide adequate cerebral perfusion pressure (CPP) to prevent cerebral ischemia or massive cerebral edema. Permissive hypotension is not recommended in TBI.

Recent emphasis in the study of resuscitation of TBI patients involves the utilization of HTS. Although not FDA approved, several animal and human models have demonstrated its benefit. HTS has been shown to decrease cerebral edema while maintaining adequate MAP and CPP. The mechanism by which HTS solution accomplishes these beneficial cerebral effects is most likely multifactorial.

The authors of "Guidelines for the Field Management of Combat-Related Head Trauma" made the following recommendations:

• Inadequate outcome clinical data exists to prefer one resuscitation fluid over another; however, HTS and colloids offer clear logistical advantage over isotonic crystalloids in a combat environment;[58]

• There is Class 1 evidence that the use of HTS is a safe alternative method of treating hypotensive TBI patients without worsening outcome;[58] and

• The authors recommended two boluses of 250 mL 5% HTS or 500 mL 3% HTS.[58]

Ware and colleagues assessed the safety and efficacy of small-volume injections of 23.4% sodium chloride solution for the treatment of intracranial hypertension in patient with TBI who became tolerant to mannitol.[59] From the study, the mean reductions in ICP after treatment were significant for both mannitol and HTS. However, the mean duration of ICP reduction was much longer for HTS (96 minutes) when compared to mannitol (59 minutes). The study suggested that 23.4% HTS is a safe and effective treatment for elevated ICP in patients after TBI.

A group that evaluated the neuronal and behavioral outcome after TBI plus hemorrhage when resuscitated with hypertonic solution of HTS, or HTS plus I-arginine, arrived at the premise that hypertonic solutions will acutely improve cerebral blood flow after TBI followed by hypotension.[60] The study stratified rats into six arms receiving different resuscitation fluids, with subsequent assessments of vestibulomotor and spatial memory functions. The study concluded that both HTS and HTS plus I-arginine were effective at promoting long-term neuronal survival and behavioral recovery.

Although existing evidence supports HTS, controversy still persists. Baker and colleagues looked at the effect of resuscitation fluid on neurologic physiology after cerebral trauma and hemorrhage.[61] Using the rat model, various resuscitation strategies (blood, normal saline, HTS, and albumin) were evaluated. MAP and cerebral oximetry were assessed in the hemorrhage group.

Table 4. Consensus View of Pre-hospital Fluid Resuscitation in Trauma Patients

1. Cannulation should take place en route to the hospital
2. Only two attempts at cannulation should be made
3. Transfer should not be delayed in an attempt to obtain intravenous access
4. Entrapped patients require cannulation at the scene
5. Normal saline is recommended as a suitable fluid for administration to trauma patients
6. Boluses of 250 mL of fluid may be titrated against the presence or absence of a radial pulse

Source: Revell M, Porter K, Greaves I. Fluid resuscitation in pre-hospital trauma care: A consensus view. *Emerg Med J* 2002;19:494-498.

The study found that regional tissue oxygen tension level in hemorrhaged animals reached significantly higher levels in the albumin-treated group compared with the normal saline and HTS groups. They concluded that albumin demonstrated the greatest beneficial effects on neurophysiology end points over crystalloid alternatives.

A recently published human study sought to answer questions regarding HTS in hypotensive head-injured patients.[62] The study demonstrated that mean ICP level dropped by 45%, and this drop persisted for 6 hours, while CPP level increased by 20%. $PbtO_2$ levels remained persistently elevated for all time points after HTS infusion. Although this study provides strong support for HTS utilization in TBI, there were no control data, and the sample size was too small to adequately power.

The use of HTS in TBI has evolved, and evidence now supports its utilization. Presently, there is a paucity of well-controlled clinical trials to determine the evidence for the best concentration, administration approach, and length of therapy.[63] Although there is no currently available randomized, controlled trial with a large enough sample size to be adequately powered, a current phase III, multi-center, randomized, controlled trial titled "Hypertonic Saline Following Traumatic Brain Injury," expected to be completed in 2010 at the University of Washington, may shed more light on the beneficial effects of HTS in TBI.

The role of HBOC in TBI continues to be evaluated despite the fact that HBOC utilization in TBI remains an exclusionary criterion in nearly every HBOC trial because of its vasoactive properties. Several studies are beginning to show its benefit in low-volume resuscitation.

King and colleagues hypothesized that low-volume resuscitation with vasoactive hemoglobin-based oxygen carrier (hemoglobin glutamer-201, HBOC-301) will improve outcome after severe TBI with hemorrhagic shock.[64] Using the swine model, they stratified anesthetized animals to receive HBOC alone, LR + HBOC, or LR + mannitol + packed RBC. They demonstrated that HBOC alone and HBOC + LR had superior outcomes. Also, lactate level and base excess corrected faster with the HBOC + LR combination despite a 40% decrease in cardiac index. Furthermore, with HBOC alone and HBOC + LR, MAP and heart rate rapidly corrected and remained normal. HBOC alone also allowed all ani-

Table 5. Pediatric Patient Systemic Responses to Blood Loss

System	Mild blood volume loss (<30%)	Moderate blood volume loss (30-45%)
Cardiovascular	Increased HR, weak, thready peripheral pulses	Markedly increased heart rate; low-normal blood pressure; narrowed pulse pressure; absent peripheral pulses, with weak, thready central pulses
Central nervous system	Anxious, irritable, confused	Lethargic, dulled response to pain
Skin	Cool, mottled; prolonged capillary refill	Cyanotic; markedly prolonged capillary refill
Urinary output	Minimal	Minimal

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mals to wean and extubate when compared to LR + mannitol + RBC. After 72 hours, the study also revealed that no HBOC-resuscitated animal had a detectable neurologic deficit.

This is a very promising animal model study. Several other recent studies have shown similar results.[65,66] However, until a controlled human study trial is performed, the utility of HBOC in TBI currently is not recommended.

Pediatric Consideration

Trauma is the leading cause of death in children age 1–14 years in the developed world. It is also the major cause of disability.[67] Thirty percent of early death in severe trauma is due to inadequate evaluation and inappropriate treatment.[67] Reduction in morbidity and mortality is dependent on early transport and appropriate resuscitation.

Skill in resuscitating the injured child includes understanding the physiologic variances. Children have excellent physiological adaptations; hence, shock may not be recognized in the early stages. Hypotension is oftentimes a late critical sign. In the pediatric circulatory system, shock may exist with a normal blood pressure. Normal systolic blood pressure could be estimated by adding 80 to age in years times two (80 + [age in years × 2]), while the diastolic blood pressure is roughly two thirds the systolic pressure. The total pediatric blood volume is estimated at 80 mL/kg; for a child to display hypotension resulting from hypovolemia, at least 25% of blood volume must have been lost.[67-69]

In a child, the decrease in cardiac output is proportional to the rate of blood volume decrease, although blood pressure may remain unchanged. Also, the stroke volume is fixed and, in the event of hypovolemia, cardiac output is maintained by increased heart rate and peripheral vascular resistance. In the presence of exhausted cardiac reserves, bradycardia indicates significantly decreased blood volume.

Fluid resuscitation in the pediatric trauma population has not changed much over the past decade. An extensive literature search revealed a paucity of articles in pediatric trauma fluid resuscitation. The goal of resuscitation in a hypovolemic injured child is restoration of normovolemia. Intravenous access in the pediatric population is often difficult and time-consuming in a volume-depleted state due to compensatory vasoconstriction. If intravenous cannulation is unsuccessful after two attempts, an intraosseous line should be established. The goal for peripheral access insertion should be 60–90 seconds. If this fails, intraosseous access should be obtained. A flow rate of about 40 mL/min can be achieved through an intraosseous line using a pressure bag.[70] The intraosseous access allows resuscitation until a definitive central vascular access can be established.

Owing to epidemiology of injury pattern in children, field fluid resuscitation may not be critical.[71] The mantra for the pre-hospital personnel should be scoop-and-run while assessing for vascular access en route to the hospital. Since children have smaller blood volume, they cannot afford to lose large volumes of blood. Scalp, neck region, penetrating truncal, and extremity injuries can produce significant amounts of blood loss, resulting in hemodynamic instability. Priority should be aggressive control of obvious bleeding. **Table 5** depicts the systematic response of pediatric patients to blood loss.

Since all pediatric trauma patients do not necessarily need resuscitation, what are the predictors of fluid resuscitation in pediatric trauma patients? ATLS guidelines are currently the standard of care for pediatric trauma care. However, ATLS applicability to pediatric patients has come under some question, since it is designed for the adult population.

Vella and colleagues performed a study to evaluate and establish the predictors of fluid resuscitation, and to determine whether all pediatric level 1 trauma victims require two intravenous accesses as per the ATLS guidelines.[71] They retrospectively reviewed charts of children younger than 18 years of age who met the criteria for level 1 trauma. Their review revealed that 70% of the patients received no fluid bolus, 20% received a single bolus, 7% received two boluses, and 3% received more than two boluses. They show that there are no statistically significant differences in fluid resuscitation or second intravenous access placement based on mechanism of injury. Age was the only predictor of second IV access placement and the injury severity score (ISS) was the only predictor of need for fluid resuscitation (not likely to be helpful in the clinical setting) They concluded that ATLS guidelines for IV access may not be appropriate for management of pediatric trauma.

The choice of fluid for pediatric resuscitation has not been

well studied except in cases of TBI. According to the excerpts from the spring 2003 International Trauma Anesthesia and Critical Care Symposium (ITACCS), crystalloids 20 mL/kg bolus in two doses should be given to the hemodynamically unstable child.[67] If there is no improvement, blood products at 10 mL/kg should be administered. Colloid should only be given as a temporizing measure while awaiting blood products. However, in burn patients, the Parkland formula using LR at 4 mL/kg/% of burn in the first day is still the most commonly utilized resuscitation modality.[72]

Although there is a paucity of research in pediatric fluid resuscitation, we can extrapolate the theory of hypotensive or small-volume resuscitation to the injured child to minimize fluid overload until control of active hemorrhage is achieved. Because of deleterious effect of hypotension to the neurologic outcome in TBI, hypotensive resuscitation is not recommended in this subset.

Complications from aggressive fluid resuscitation in children have been reported. One group reported a case of secondary abdominal compartment syndrome in a case of pediatric trauma shock resuscitation.[73] The case was that of a 17-year-old trauma patient with ongoing blood loss from a lacerated superficial temporal artery who received aggressive crystalloid resuscitation before arrival at a designated trauma hospital.

In pediatric head injury, the goal of resuscitation is to prevent secondary brain injury that could result from hypotension, hypoxia, anemia, and hyperglycemia. To accomplish this goal, CPP should be optimized, accounting for age-related differences in optimal CPP goal.[74] According to ITACCS excerpts, CPP ought to be maintained at greater than 40 mmHg in younger children, and greater than 50 mmHg in older children and adolescents.[75]

The use of HTS in pediatric TBI has also gained favor. A prospective, randomized, controlled study of fluid management in children with severe head injury comparing LR solution to hypertonic saline, performed at a level III pediatric intensive care unit, concluded that treatment with hypertonic saline is superior to that of LR solution.[76] An increase in serum sodium concentration correlates well with lower ICP and higher CPP. The study also shows that the children with HTS require fewer interventions, have fewer complications, and have shorter stays in the intensive care unit.

Khanna and colleagues evaluated the effect of prolonged infusion of 3% HTS and sustained hypernatremia on refractory intracranial hypertension in pediatric TBI.[77] In the study, they treated 10 pediatric TBI patients with increased ICP refractory to conventional treatment with titrated infusion of 3% normal saline to achieve a sodium level that would maintain ICP less than 20 mmHg. They demonstrated a statistically significant decrease in ICP and increase in CPP.[77] Based on these results, they concluded that increase in serum sodium concentration significantly decreased ICP and increased CPP, and that hypernatremia and hyperosmolarity are safely tolerated in pediatric patients with TBI.[77]

Conclusion

The review of the current body of literature is beginning to shed light on the future direction of resuscitation. Presently, the general consensus based on the available data from the last 10 years is to avoid under-resuscitation or over-resuscitation. The premise behind this is that under-resuscitation promotes end organ ischemia, while over-resuscitation may lead to re-bleeding, hemodilution, and coagulation abnormalities.[30] The goal of resuscitation should be to accomplish a perfusing blood pressure. The ideal blood pressure end point for non-head-injured patients should be guided by the radial pulse, the presence of which suggests systolic blood pressure of approximately 80–90 mmHg. Based on this parameter, if radial pulse cannot be palpated, fluid should be given until it is palpated. With this parameter, we can resuscitate to perfuse while minimizing the consequences of under- or over-resuscitation.

Regarding resuscitation fluids, clarity is emerging while the search for the ideal resuscitative fluid continues. From available data, initial resuscitation with large-volume isomeric LR solution could promote reperfusion injury. This is due to the effect of the D-isomer on neutrophil oxidative burst, endothelial damage, and the clearance of lactic acids. However, these adverse effects were not seen with the L-isomer solution. Based on this information, it could be concluded that the L-isomer LR solution should be utilized in place of the racemic mixture. However, until adequately powered, randomized, controlled trials are performed in human subjects, it will be difficult to propose changes to the ATLS guideline that recommends racemic LR as the initial resuscitation fluid of choice.

HTS has also shown significant promise, and it's slowly becoming the fluid of choice in Europe and in the military. In the era of low-volume resuscitation, its ability to act as a volume expander by rapidly mobilizing endogenous fluid, its immunomodulatory and hemodynamic effects, and the requirement of only a small volume to effectively restore cardiovascular function makes it an ideal choice for resuscitation. Although not FDA-approved yet, its ability to increase CPP while decreasing ICP in TBI patient has been well documented. It should be the fluid of choice in TBI, and this utility can be extrapolated to include non-head-injured trauma patients.

The search for the elusive ideal fluid for resuscitation is more promising than ever before. The ideal resuscitation fluid should have the following characteristics: capable of carrying oxygen, little or no effect on coagulation, inexpensive, non-allergic or antigenic, and a relatively long shelf-life at room temperature. HBOC has almost all these characteristics, and may hold the future of resuscitation.

The concerns about the potential side effects (vascular toxicity, pulmonary and systemic hypertension, and myocardial infarction) are slowly being resolved. These side effects are due to the scavenging properties of free deoxygenated hemoglobin on nitric oxide, which renders it unavailable for blood vessel dilation. A novel technology that allows free nitrite or nitrites methemoglobin to be added to stromal-free HBOC will lead to the elimination of the side effects that prevent its FDA approval. When free nitrites are added to HBOC, nitric oxides (NO and NO_2O_3) are produced. These by-products are able to escape the scavenging properties of free deoxyhemoglobin, and thus are available to dilate blood ves-

sels. The ability to produce free nitric oxide will eliminate the concerns of systemic or pulmonary hypertension and myocardial infarction associated with HBOC.[78]

The more clinical and laboratory research is performed, the more fuel is added to the controversy regarding choice of fluid, how fast and how much volume should be infused, and the ideal parameter to guide resuscitation strategies. Since most of these studies do not include human trials, it's hard to extrapolate their findings to clinical practice. Until we have adequately paired randomized, controlled studies involving human subjects to validate the finding in animals, the controversy will continue to rage. HTS and HBOC may be the future of resuscitation, since more promising human trials are beginning to confirm results from animal models.

References

1. Mizushima Y, Tohira H, Mizobata Y, et al. Fluid resuscitation of trauma patients: How fast is the optimal rate? *Am J Emerg Med* 2005;23:833-837.
2. American College of Surgeons Committee on Trauma. Advanced Trauma Life Support for Doctors: Student Course Manual, 7th edition. Chicago,IL: American College of Surgeons; 2004.
3. Greaves I, Porter KM, Revell MP. Fluid resuscitation in pre-hospital trauma care: A consensus view. *J R Coll Surg Edinb* 2002;47:451-457.
4. Boldt J. Fluid choices for resuscitation in trauma. *International TraumaCare (ITACCS)* 2008;18:57-65.
5. Shires T, Colin D, Carrico J, et al. Fluid therapy in hemorrhagic shock. *Arch Surg* 1969;88:688-693.
6. Skellet S, Mayer A, Durward A, et al. Chasing the base deficit: Hyperchloremic acidosis following 0.9% saline resuscitation. *Arch Dis Child* 2000;83:514-516.
7. Rudra A, Chatterjee S, Sengupta S, et al. Fluid resuscitation in trauma. *Indian J Crit Care Med* 2006;10:241-249.
8. Coimbra R, Doucet JJ, Bansal V. Resuscitation strategies in hemorrhagic shock–Hypertonic saline revisited. *Emergency Medicine and Critical Care Review* 2007:1-8.
9. Rhee P, Burris D, Kaufmann C, et al. Lactated Ringer's solution resuscitation causes neutrophil activation after hemorrhagic shock. *J Trauma* 1998;44:313-319.
10. Alam HB, Stanton K, Kaustova E, et al. Effect of different resuscitation strategies on neutrophil activation in a swine model of hemorrhagic shock. *Resuscitation* 2004;60:91-99.
11. Kiraly LN, Differding JA, Enomoto TM, et al. Resuscitation with normal saline (NS) vs lactated ringers (LR) modulates hypercoagulability and leads to increased blood loss in an uncontrolled hemorrhagic shock swine model. *J Trauma* 2006;61:57-64.
12. Koustova E, Stanton K, Gushchin V, et al. Effects of lactated Ringer's solutions on human leukocytes. *J Trauma* 2002;52:872-878.
13. Savage SA, Fitzpatrick CM, Kashyap VS, et al. Endothelial dysfunction after lactated Ringer's solution resuscitation for hemorrhagic shock. *J Trauma* 2005;59:284-290.
14. Jaskille A, Kaustova E, Rhee P, et al. Hepatic apoptosis after hemorrhagic shock in rats can be reduced through modifications of conventional Ringer's solution. *J Am Coll Surg* 2006;202:25-35.
15. Ayuste EC, Chen H, Kaustova E, et al. Hepatic and pulmonary apoptosis after hemorrhagic shock in swine can be reduced through modifications of conventional Ringer's solution. *J Trauma* 2006;60:52-63.
16. Angle N, Hoyt DB, Coimbra R, et al. Hypertonic saline resuscitation diminishes lung injury by suppressing neutrophil activation after hemorrhagic shock. *Shock* 1998;101:164-170.
17. Riddez L, Drobin D, Sjostrand F, et al. Low dose hypertonic saline dextran reduces the risk of lethal rebleeding in uncontrolled hemorrhage. *Shock* 2002;17:377-382.
18. Spahn SR, Rossaint R. Coagulopathy and blood component transfusion in trauma. *Br J Anaesth* 2005;95:130-139.
19. Haas T, Fries D, Innerhofer P, et al. Less impairment on hemostasis and reduced blood loss in pigs after resuscitation from hemorrhagic shock using small-volume concept with hypertonic saline/hydroxylethyl starch as compared to administration 4% gelatin or 6% hydroxylethyl starch solution. *Anesth Analg* 2008;106:1078-1086.
20. Rhee P, Kaustova E, Alam HB. Searching for the optimal resuscitation method: Recommendation for the initial fluid resuscitation of combat casualties. *J Trauma* 2003;54:S52-62
21. Cochrane Injury Group Albumin Reviewers. Human albumin administration in critically ill patients: Systemic review of randomized control trials. *BMJ* 1998;317:235-240.
22. The SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the ICU. *N Engl J Med* 2004;350:2247-2256.
23. Wilkes MM, Navickis RJ. Patient survival after human albumin administration. *Ann Intern Med* 2001;135:149-154
24. Grocott MPW, Hamilton MA. Resuscitation fluids. *Vox Sang* 2001;82:1-8.
25. Boldt J. Fluid choice for resuscitation of the trauma patients: A review of physiological, pharmacological, and clinical evidence. *Can J Anaesth* 2004;51:500-513.
26. Ferreira EL, Terzi RG, Silva WA, et al. Early colloid replacement therapy in a near fatal model of hemorrhagic shock. *Anesth Anal* 2005;101:1785-1791.
27. Swank K. Hemoglobin Based Oxygen Carriers in Trauma. 2004 Colorado Review of Anesthesiology & Ski Holiday. Available at www.Cucrash.com/Handouts04/HBOCsSwank.pdf. Accessed 3/31/2009.
28. Moore FA, Moore EE, Sauaia A. Blood transfusion: An independent risk factor for post injury multiple organ failure. *Arch Surg* 1996;132:620-625.
29. Maxwell RA, Gibson JB, Fabian TC, et al. Resuscitation of severe chest trauma with four different hemoglobin-based oxygen carrying solutions. *J Trauma* 2000;49:200-209.
30. Arnoldo B, Minei J. Potential of hemoglobin-based oxygen carrier in trauma patients. *Curr Opin Crit Care* 2001;7:431-436.
31. Gould SA, Moore EE, Hoyt DB, et al. The first randomized trial of human polymerized hemoglobin as a blood substitute in acute trauma and emergent surgery. *J Am Coll Surg*1998;187:113-122.
32. Gould SA, Moore EE, Hoyt DB, et al. The life sustaining capacity of human polymerized hemoglobin when red cells might be unavailable. *J Am Coll Surg* 2002;195:445-455.
33. Johnson J, Moore EE, Gonzales RJ, et al. Resuscitation with a blood substitute abrogates pathologic post injury neutrophil cytotoxic function. *J Trauma* 2001;50:449-456.
34. Johnson JL, Moore EE, Gonzalez RJ, et al. Alteration of the post injury hyperinflammatory response by means of resuscitation with a red cell substitute. *J Trauma* 2003;54:133-140.
35. Northfield Laboratories releases summary observations from its elective surgery trial [news release]. Evanston, IL: Northfield Laboratories Inc.; 2006. Available at http://phx.corporate-ir.net/phoenix. zhtml?c=91374&p=irol-

newsArticle_print&ID=833808&highlight=. Accessed April 1, 2009.
36. Riddez L, Johnson L, Hahn RG. Central and regional hemodynamics during crystalloid fluid therapy after uncontrolled intra-abdominal bleeding. *J Trauma* 1998;44:433-439.
37. McGee S, Abernethy WB, Simmel DL. Is this patient Hypovolemic? *JAMA* 1999;281:1022-1029.
38. Deakin CD, Low JL. Accuracy of the Advanced Trauma Life support guidelines for predicting systolic blood pressure using carotid, femoral, and radial pulses: Observational study. *BMJ* 2000;321:673-674.
39. Pepe PE, Mosesso VN, Falk JL, et al. Pre-hospital fluid resuscitation of the patient with major trauma. *Prehosp Emerg Care* 2002;6:81-91.
40. Hoyt DB. Fluid resuscitation: The target from an analysis of trauma systems and patient survival. *J Trauma* 2003;54:S31-S35.
41. Fowler R, Pepe PE. Pre-hospital care of patient with major trauma. *Emerg Med Clin North Am* 2002;20:953-974.
42. Dretzke J, Burls A, Bayliss S, et al. The clinical effectiveness of pre-hospital intravenous fluid replacement in trauma patients without head injury: A systemic review. *Trauma* 2006;8:131-141.
43. Dula DJ, Wood GC, Rejmer AR, et al. Use of prehospital fluid in hypotensive blunt trauma patients. *Prehosp Emerg Care* 2002;6:417-420
44. Berlot G, Bacer B, Gullo A. Controversial aspects of the pre-hospital trauma care. *Crit Care Clin* 2006;22:457-468.
45. Soreide E, Deakin CD. Pre-hospital fluid therapy in the critically injured patient – A clinical update. *Injury* 2005;36:1001-1010.
46. Revell M, Porter K, Greaves I. Fluid resuscitation in pre-hospital trauma care: A consensus view. *Emerg Med J* 2002;19:494-498.
47. Fowler R, Pepe PE. Fluid resuscitation of the patient with major trauma. *Curr Opin Anaesthesiol* 2002;15:173-178.
48. Cannon W, Fraser J, Cowell E. Preventative treatment of wound shock. *JAMA* 1918;70:618-621.
49. Dutton RP, MacKenzie CF, Scalea TM. Hypotensive resuscitation during active hemorrhage: Impact on in-hospital mortality. *J Trauma* 2002;52:1141-1146.
50. Holmes JF, Sackles JC, Lewis G, et al. Effects of delaying fluid resuscitation on an injury to the systemic arterial vasculature. *Acad Emerg Med* 2002;9:267-274.
51. Krausz MM, Bashenko Y, Hirsh M, et al. Crystalloid and colloid resuscitation of uncontrolled hemorrhagic shock following massive splenic injury. *Shock* 2001;16:383-388.
52. Abu-Hatoum O, Bashenko Y, Hirsh M, et al. Continuous fluid resuscitation and splenectomy for treatment of uncontrolled hemorrhagic shock after massive splenic injury. *J Trauma* 2002;52:253-258.
53. Lu YQ, Cai XJ, Gu LH, et al. Experimental study of controlled fluid resuscitation in the treatment of severe and uncontrolled hemorrhagic shock. *J Trauma* 2007;63:798-804.
54. Cooper JD, Myles PS, McDermott FT, et al. Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury. *JAMA* 2004;291:1350-1357.
55. Wood RLI, McCrea JD, Wood LM, et al. Clinical and cost effectiveness of post-acute neurobehavioral rehabilitation. *Brain Injury* 1999;13:69-88.
56. U.S. Department of Health and Human Services, National Institutes of Health. Rehabilitation of persons with traumatic brain injury. *NIH Consens Statement* 1998;16:1-41.
57. Bullock RM, Chesnut RM, Clifton GL. Management and prognosis of severe traumatic brain injury. *J Neurotrauma* 2000;17:449-553.
58. Knuth T, Letarte PB, Ling G, et al. *Guidelines for field management of combat related head trauma: Fluid resuscitation.* New York (NY): Brain Trauma Foundation; 2005:13.
59. Ware ML, Nemani VM, Meeker M, et al. Effects of 23.4% sodium chloride solution in reducing intracranial pressure in patients with traumatic brain injury: A preliminary study. *Neurosurgery* 2005;57:727-736.
60. Sell SL, Avila MA, Yu G, et al. Hypertonic resuscitation improves neuronal and behavioral outcomes after traumatic brain injury plus hemorrhage. *Anesthesiology* 2008;108:873-881.
61. Baker AJ, Park E, Hare GM, et al. Effects of resuscitation fluid on neurologic physiology after cerebral trauma and hemorrhage. *J Trauma* 2008;64:348-357.
62. Pascual JL, Maloney-Wilenski E, Reilly PM, et al. Resuscitation of hypotensive head injured patients: Is hypertonic saline the answer? *Am Surg* 2008;74:253-259.
63. Forsyth LL, Liu-DeRuke X, Parker D Jr, et al. Role of hypertonic saline for the management of intracranial hypertension after stroke and traumatic brain injury. *Pharmacotherapy* 2008;28:469-484.
64. King DR, Cohn SM, Proctor KG. Resuscitation with hemoglobin based oxygen carrier after traumatic brain injury. *J Trauma* 2005;59:553-560.
65. Rosenthal G, Morabito D, Cohen M, et al. Use of hemoglobin based oxygen cCarrier-201 Solution to improve resuscitation parameters in a swine model of traumatic brain injury and hemorrhage: Laboratory investigation. *J Neurosurg* 2008;108:575-587.
66. Stern S, Rice J, Philbin N, et al. Resuscitation with hemoglobin based oxygen carrier (HBOC-201) in a swine model with severe uncontrolled hemorrhage with traumatic brain injury. *Shock* 2008;19. (E-published ahead of print.)

CNE/CME Objectives

Upon completing this program, the participants will be able to:

a.) discuss conditions that should increase suspicion for traumatic injuries;
b.) describe the various modalities used to identify different traumatic conditions;
c.) cite methods of quickly stabilizing and managing patients; and
d.) identify possible complications that may occur with traumatic injuries.

CNE/CME Instructions

Physicians and nurses participate in this continuing medical education/continuing 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 test 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 provided and return it in the reply envelope provided in order to receive a letter of credit.** When your evaluation is received, a letter of credit will be mailed to you.

67. Johnson C. Fluid management of the injured child. *International Trauma Anesthesia Critical Care Symposium (ITACCS)* 2003:57.
68. Lee GM. Pediatric trauma. www.ualberta.ca/pediatri/clinical/pedtraum.htm.
69. Schweer L. Pediatric trauma resuscitation: Initial fluid management. *J Infus Nurs* 2008;31:104-111.
70. Smith R, Davis N, Bouamra O, et al. Utilization of intra-osseous infusion in the resuscitation of major trauma patient. *Injury* 2005;36:1034-1038.
71. Vella AE, Wang VJ, McElderry C. Predictors of fluid resuscitation in pediatric trauma patient. *J Emerg. Med* 2006;31:151-155.
72. Purdue G. Early care of pediatric burn patient. *International Trauma Anesthesia Critical Care 16th Spring Symposium,* 2003:57-65.
73. Morrell BJ, Vinden C, Singh RN, et al. Secondary abdominal compartment syndrome in a case of pediatric trauma resuscitation. *Pediatr Crit Care Med* 2007;8:67-70.
74. Orliaguet GA, Meyer PG, Baugnon T. Management of critically ill children with traumatic brain injury. *Paediatr Anaesth* 2008;18:455-461.
75. Berman J. Pediatric head injury: Where have we been, where are we going? *International Trauma Anesthesia Critical Care 16th Spring Symposium,* 2003:57.
76. Simma B, Burger R, Falk M, et al. A prospective, randomized, and controlled study of fluid management in children with severe head injury: Lactated Ringer's solution versus hypertonic saline. *Crit Care Med* 1998;26:1265-1270.
77. Khanna S, Davis D, Peterson B, et al. Use of hypertonic saline in treatment of severe refractory post traumatic intracranial hypertension in pediatric traumatic brain injury. *Crit Care Med* 2000;28:1144-1151.
78. Ferguson S. Nitrites and nitrite-methemoglobin therapy to detoxify stroma free hemoglobin based blood substitutes. *Federal Register* 2008;73(75):20929-20930.

CNE/CME Questions

1. The concern for hemoglobin-based oxygen carriers' utility in traumatic brain injury patient is:
   a. Its high oxygen affinity
   b. Its negative effect on cerebral perfusion pressure
   c. Its vasoactive properties
   d. Its immunomodulating properties

2. According to Vella et al, the most important predictor of pediatric fluid resuscitation is:
   a. Age
   b. Revised trauma score
   c. Injury severity score
   d. Mechanism of injury

3. In the head-injured younger child, the goal for cerebral perfusion pressure should be:
   a. 10–20 mmHg
   b. 20–25 mmHg
   c. Greater than 40 mmHg
   d. Greater than 60 mmHg

4. According to the ATLS guidelines for pediatric fluid resuscitation, if after two boluses of crystalloid are given the patient is still hypotensive, the next choice is:
   a. blood at 20 mL/kg.
   b. colloid at 20 mL/kg.
   c. blood at 10 mL/kg.
   d. colloid at 10 mL/kg.

5. All of the following are characteristics of D-isomer Ringer's lactate that have deleterious effect on resuscitation *except*:
   a. inhibits lactic acid clearance
   b. stimulates neutrophil oxidative bursts
   c. damages the endothelium
   d. inhibits neutrophil oxidative burst

6. The exception to the "scoop-and-run" mantra for pre-hospital personnel is the:
   a. Hypotensive blunt trauma patient
   b. Hypotensive penetrating trauma patient
   c. Multi-trauma head injury victim
   d. Entrapped patient

7. Using the radial pulse as a parameter for adult fluid resuscitation, the presence of pulse is equivalent to what systolic blood pressure?
   a. 60–70 mmHg
   b. 70–80 mmHg
   c. 80–90 mmHg
   d. Greater than 100 mmHg

8. Which of following are potential side effects of hemoglobin-based oxygen carriers (HBOC)?
   a. Nephrotoxicity
   b. Vasoconstriction
   c. Methemoglobinemia
   d. All of the above

9. The characteristics of hypertonic saline that make it a promising resuscitative fluid include all of the following *except*:
   a. Direct vasodilatory effect
   b. Reduction of venous capacitance
   c. Positive ionotropic effect through action on myocardial cells
   d. Increasing tissue edema

10. Based on the available data, the current resuscitation trend in hemorrhaging trauma patients includes all the following *except*:
    a. Low-volume resuscitation
    b. Permissive hypotension
    c. Carefully monitored resuscitation
    d. Aggressive fluid resuscitation of patients with a blood pressure of 90 mmHg

Answers: 1. C; 2. C; 3. C; 4. C; 5. D; 6. D; 7. C; 8. D; 9. D; 10. D

In Future Issues: **Organ Donation and Procurement**

Trauma Reports
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CNE/CME Evaluation — Fluid Management in the Adult and Pediatric Trauma Patient
Please take a moment to answer the following questions to let us know your thoughts on the CNE/CME program. Fill in the appropriate space and return this page in the envelope provided. **You must return this evaluation to receive your letter of credit. ACEP members — Please see reverse side for option to mail in answers.** Thank you.

CORRECT ● **INCORRECT** ⊘ ✓ ✗ ⚠

1. In which program do you participate? ○ CNE ○ CME
2. If you are claiming physician credits, please indicate the appropriate credential: ○ MD ○ DO ○ Other _____
3. If you are claiming nursing contact hours, please indicate your highest credential: ○ RN ○ NP ○ Other _____

After participating in this program, I am able to:	**Strongly Disagree**	**Disagree**	**Slightly Disagree**	**Slightly Agree**	**Agree**	**Strongly Agree**
4. Discuss conditions that should increase suspicion for traumatic injuries.	○	○	○	○	○	○
5. Describe the various modalities used to identify different traumatic conditions.	○	○	○	○	○	○
6. Cite methods of quickly stabilizing and managing patients.	○	○	○	○	○	○
7. Identify possible complications that may occur with traumatic injuries.	○	○	○	○	○	○
8. The test questions were clear and appropriate.	○	○	○	○	○	○
9. I am satisfied with customer service for the CNE/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 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 CNE/CME program?

_____

I have completed the requirements for this activity.

Name (printed) _____ **Signature** _____

Nursing license number ***(required for nurses licensed by the state of California)*** _____

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Optional for ACEP members: In accordance with ACEP requirements, below we provide the option for ACEP members to submit their answers for this CME activity. If you wish to submit answers for this activity, please refer to this issue (Vol. 10, No. 3) and circle the correct responses.

1. A
   B
   C
   D

2. A
   B
   C
   D

3. A
   B
   C
   D

4. A
   B
   C
   D

5. A
   B
   C
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6. A
   B
   C
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7. A
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8. A
   B
   C
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9. A
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   C
   D

10. A
    B
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    D

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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 _____

	Strongly Disagree	Disagree	Slightly Disagree	Slightly Agree	Agree	Strongly Agree
After participating in this program, I am able to:						
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. Would you prefer to test with each issue or by semester?_____ by issue_____by semester (check one)
15. Do you have any general comments about the effectiveness of this CME program?

_____

I have completed the requirements for this activity.

Name (printed) _____ **Signature**_____

111. A B C D E 112. A B C D E 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 E
118. A B C D 119. A B C D E 120. A B C D