A 30-year-old man with no notable medical history presented to the emergency department with nausea, emesis, and pain in his chest and between the shoulder blades. Three days before presentation, he noted the onset of back pain with associated vomiting and loose stools. He reported feeling somewhat improved over the course of the night into the next morning but subsequently had development of diaphoresis with return of the back pain. The recurrent episode was associated with chest pain described as nonpositional, nonradiating substernal heaviness. He had no cardiovascular risk factors.

On physical examination, he was afebrile, with a pulse rate of 72 beats/min, blood pressure of 113/77 mm Hg, respiratory rate of 16 breaths/min, and oxygen saturation of 100% while breathing room air. Findings on physical examination, including cardiopulmonary assessment, were unremarkable. Basic laboratory studies yielded the following values (reference ranges were unremarkable): hemoglobin, 12.7 g/dL; leukocytes, 9.2 × 10^9/L (3.5-10.5 × 10^9/L); platelet count, 138 × 10^9/L (150-450 × 10^9/L); erythrocyte sedimentation rate, 22 mm/h (0-22 mm/h); and C-reactive protein, 43 mg/L (≤8 mg/L). His troponin T level increased from 1.28 ng/mL (<0.01 ng/mL) at initial measurement to 1.80 ng/mL at 3 hours and 1.87 at 6 hours, a notable delta troponin.

Initial electrocardiography (ECG) yielded marked evidence of ischemia with ST-segment elevations in the inferior and anterolateral leads. A tombstone pattern was noted on the inferior leads with near-linear ST segments. Patterns on the anterior leads were less dramatic, with concave ST-segment elevations (Supplemental Figure, available online at http://www.mayoclinicproceedings.org). Transthoracic echocardiography (TTE) indicated a left ventricular ejection fraction (EF) of 53% and inferolateral hypokinesis at the mid and base aspects of the heart, and the entire apex was hypokinetic.

1. On the basis of the patient's history and physical examination findings, which one of the following diagnoses is of most concern?

   a. Acute coronary syndrome (ACS)
   b. Pericarditis
   c. Myocarditis
   d. Stress-induced cardiomyopathy
   e. Gastroenteritis

The patient presented with acute chest pain, troponin elevation, and ECG changes concerning for ACS, specifically, acute ST-segment elevation myocardial infarction (STEMI) due to intracoronary blockage. It is critical that ACS first be ruled out because of the potential for serious myocardial injury, especially if there are delays in adequate treatment. The patient's history suggests a viral prodrome, with symptoms of vomiting and diarrhea. Despite negative findings on the physical examination and echocardiography, pericarditis and myocarditis should be considered high in the differential diagnosis of this patient; however, based on his presentation, they should only be entertained after ruling out ACS because the greatest benefits of ACS therapy are seen early in the disease process. Although his elevated inflammatory markers support the diagnosis of a carditis, they are nonspecific and can also be elevated in ACS. Stress-induced cardiomyopathy is a diagnosis of exclusion and should not be considered before further work-up. Criteria put forth for diagnosis have included transient hypokinesis of the mid left ventricular segments, regional wall motion abnormalities beyond a single epicardial coronary distribution, stressful trigger, absence of coronary disease, and absence of pheochromocytoma or myocarditis. The increase in the cardiac biomarkers in our patient does not aid in diagnosis, how-ever, because an evolving cardiac biomarker panel can be seen in both ACS and stress-induced cardiomyopathy. The patient reported gastrointestinal symptoms in the days before his presentation, which suggests a pathogen-induced enteritis. At the time of his presentation, these symptoms had largely resolved. Although he had continued nausea and vomiting, the overall acute clinical picture is more concerning for ACS.
The patient was stabilized, given morphine for the pain, and urgently evaluated by the cardiology service for further recommendations.

2. Given the suspected diagnosis, which one of the following is the most important next step in the management strategy?
   a. Initiation of intravenous lidocaine for the patient’s increased risk of ventricular arrhythmias
   b. Nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine
   c. Admission to a telemetry-monitored unit with serial troponin measurements and ECGs
   d. Dual antiplatelet therapy, symptom control, and catheterization laboratory activation
   e. Initiation of statin therapy, β-blockade, and angiotensin-converting enzyme (ACE) inhibition

During an acute ischemic event, a patient is at a high risk of lethal ventricular arrhythmias including ventricular fibrillation and tachycardia. However, there is currently no role for prophylactic lidocaine in this situation. Conservative management and treatment with NSAIDs and colchicine is recommended in a patient with confirmed pericarditis. At this point, there is still high enough suspicion for ACS that this would not be the best next step. The patient will ultimately require admission to a telemetry-monitored unit for close monitoring of arrhythmias, but coronary catheterization should be performed first. Furthermore, he has already had 3- and 6-hour troponin measurements that indicated a marked change. No further monitoring of troponins would be necessary at this juncture. His presenting ECG meets criteria for STEMI; serial ECG would only delay adequate treatment. This patient is best treated with dual antiplatelet therapy as well as heparin, symptom control, and immediate activation of the catheterization laboratory for alleviation of a possible coronary occlusion and percutaneous intervention as needed. Statin therapy, ACE inhibitors, and β-blockers are indicated in most cases of identified ACS. However, β-blockers should be avoided in patients with cardiogenic shock. ACE inhibitors are specifically indicated for a large anterior myocardial infarction or if the EF is less than 40%. Percutaneous coronary intervention is the treatment of choice, and the aforementioned interventions need not be performed before the procedure. 

Coronary angiography revealed normal coronary arteries. The patient’s chest pain abated, and ECG documented resolution of ST-segment elevations over time.

3. Because the work-up thus far has yielded inconclusive results, which one of the following would be the best next step in establishing a diagnosis?
   a. Endomyocardial biopsy
   b. Cardiac magnetic resonance imaging (MRI)
   c. Transesophageal echocardiogram
   d. Pericardial biopsy
   e. Catheterization of the right side of the heart

Two important clinical scenarios in which endomyocardial biopsy should be highly considered are fulminant myocarditis or suspected giant cell myocarditis. New-onset heart failure of less than 2 weeks with a dilated left ventricle or hemodynamic compromise and patients who do not respond to usual care within 1 to 2 weeks should also be considered for biopsy. Our patient was clinically stable and did not fit into these categories. Cardiac MRI is being used increasingly for the evaluation of nonischemic causes of cardiac biomarker elevations, and in this patient without coronary disease, this test would be the ideal next step in establishing a diagnosis. Transesophageal echocardiography is unlikely to contribute much more information than that already obtained on initial TTE and should only be entertained if severe valvular disease or endocarditis is suspected. Pericardial biopsy could be considered if recurrent pericarditis or pericardial effusions were evident, especially if there was a high suspicion of malignancy. That was not the case in this patient. In this setting, catheterization of the right side of the heart would not add any further diagnostic value beyond the Doppler hemodynamic assessment provided by the TTE. In cases in which intracardiac shunts or pulmonary hypertension is suspected or there is discordance between clinical and noninvasive imaging findings, catheterization of the right side of the heart may be of
value in further clarification of hemodynamic status.

The patient underwent MRI, which revealed mild global hypokinesis, an EF of 49%, and patchy delayed enhancement involving mostly the epicardial regions at the apex. The distribution of enhancement was most suggestive of myocarditis.

4. Which one of the following viral organisms is least commonly implicated in viral myocarditis?
   a. Hepatitis C virus
   b. Coxsackie B virus
   c. Adenovirus
   d. Parvovirus B19
   e. Rotavirus

Viruses continue to be an important cause of myocarditis. Cultures, serology, and polymerase chain reaction have implicated numerous viruses as causative agents, and viruses are identified in about one-third of patients with myocarditis. Recent studies have implicated hepatitis C as an etiology. Studies have also shown shifts in frequently encountered organisms. From the 1950s to the 1990s, Coxsackie B virus was reported to be most prevalent. The prevalence shifted to adenovirus in the 1990s, and more recently, parvovirus B19 is becoming more commonly recognized. There are no definitive studies identifying rotavirus as a causative agent in myocarditis at this time.

5. Which one of the following would be the best treatment option in this patient with the suspected diagnosis of myocarditis?
   a. Antiviral therapy with ribavirin or interferon alfa
   b. Immunosuppressive therapy including corticosteroids and cyclosporine
   c. Conservative therapy with aspirin and NSAIDs
   d. Intravenous immunoglobulins
   e. Dual antiplatelet therapy with clopidogrel and aspirin for 6 months

Currently, there is no role for antiviral, immunosuppressive, or intravenous immunoglobulin therapy in the treatment of myocarditis. In most patients, especially those with few clinical sequelae, conservative therapy would be the treatment of choice. Dual antiplatelet therapy would be indicated if the patient had coronary disease or had stenting during percutaneous coronary intervention.

The patient ultimately did well on conservative therapy. Because his EF was relatively preserved, initiation of a heart failure medication regimen was not indicated. Nonsteroidal anti-inflammatory agents and aspirin were prescribed, and we recommended that he avoid exercise for 4 weeks because patients with acute myocarditis should refrain from excessive exertion or competitive athletics for a period of 1 to 3 months. Recovery of ventricular function is also recommended before returning to sports. Follow-up and repeated cardiac MRI indicated resolving myocarditis and an EF of 63%, and no further symptoms were reported.

DISCUSSION
Myocarditis simply means inflammation of the myocardium. It can have many etiologies and may have a wide array of presentations. The established histologic classification of myocarditis includes the Dallas criteria, in which an inflammatory infiltrate must be present. Although this system is useful, it has somewhat fallen out of favor because of concerns regarding diagnostic accuracy, as well as its low sensitivity with ranges of 35% to 60% in some studies. Clinical pathologic classification of myocarditis has also emerged and provides the added benefit of combining clinical and histologic features. Categories include fulminant, acute, chronic active, and chronic persistent myocarditis.

In fulminant myocarditis, the patient is usually acutely ill. It often presents with acute heart failure up to 2 weeks after a viral prodrome. Cardiac function may improve if the patient survives the acute illness. Acute myocarditis presents with ventricular dysfunction and may progress to dilated cardiomyopathy. Chronic active myocarditis can be more insidious in onset. Patients may have multiple relapses and development of ventricular dysfunction with chronic inflammatory changes. Chronic persistent myocarditis is similar to chronic active myocarditis in onset, but ventricular dysfunction is usually absent. It may be characterized by cardiac symptoms such as chest pain and palpitations.

There are a wide variety of disorders and presentations that have been linked to myocarditis. The classic presentation is acute heart
failure due to a viral source. Causative agents have shifted from enteroviruses to parvoviruses, and more recently, hepatitis C virus and human herpesvirus 6 have emerged as etiologies. Other commonly seen etiologies include human immunodeficiency virus, cytomegalovirus, and bacterial infections such as Borrelia burgdorferi and Lyme disease. Drug reactions, eosinophilia, giant cells, sarcoidosis, and amyloidosis have been seen as causative etiologies as well. Presentations can be highly variable and include overt heart failure with cardiovascular collapse, chest pain, pericarditis, sudden cardiac death, and arrhythmias. Unfortunately, symptomatology can be as vague as excessive fatigue and exercise intolerance.

A definitive diagnosis is classically established by endocardial biopsy. However, it is not routinely performed unless giant cell myocarditis is strongly suspected because patients with an improving clinical course often do not warrant the risks incurred with this procedure. Furthermore, cardiac MRI, which can display myocardial edema and necrosis, has become increasingly useful in assisting in the diagnosis of myocarditis. Specifically, studies have found that combining T2-weighted and late gadolinium-enhanced (LGE) imaging yields up to 76% sensitivity and 96% specificity in the identification of myocarditis. Although LGE imaging may also reveal abnormalities in ischemic cardiac disease, they can usually be distinguished from myocarditis on the basis of the distribution within the heart. In myocarditis, LGE imaging reveals involvement of the epicardium and mid myocardium, whereas in ischemic disease, it usually involves the endocardium.

Therapy for myocarditis is largely supportive and aimed at preserving left ventricular function. Standard heart therapy recommendations such as ACE inhibitors, β-blockers, and diuretics as needed are the mainstay of treatment. Antiviral therapy has only a limited role in treating myocarditis. Some possible benefit has been found in animal models, but only if antiviral therapy is started soon after viral exposures. Very small case series studying ribavirin in acute fulminant myocarditis have found some benefit, but antiviral therapy would not be a treatment of choice in most cases. Intravenous immunoglobulin therapy does have known antiviral properties; however, studies into its role in viral myocarditis are sparse, and there is no evidence to support its use.

The role of immunosuppression in viral myocarditis is an evolving field of study. Because the host immune response is believed to be largely responsible for the clinical sequelae seen in viral myocarditis, it is hypothesized that suppressing the immune response may halt a patient’s declining clinical course. However, studies thus far have revealed no major benefit with drugs such as corticosteroids and azathioprine as treatment for most cases of myocarditis. The one exception is in cases of giant cell myocarditis. A clear benefit has been seen in patients with the disease because they do respond to multiagent immunosuppression.

The overall prognosis of fulminant myocarditis is relatively good. Patients may present in a serious condition but with appropriate management have a high likelihood of recovery. There is some difficulty in accurately determining the long-term consequences in patients with myocarditis, however. Patients with a more stable clinical presentation are less likely to undergo biopsy and receive only a presumptive diagnosis, as in our patient. As such, the true long-term consequences of biopsy-proven myocarditis are based on limited cases and are difficult to fully ascertain.

Myocarditis is a disease that can have numerous etiologies and a wide array of presentations. This case illustrates that even in a patient with what appears to be acute STEMI, an index of suspicion should be retained for other possible diagnoses such as myocarditis.

SUPPLEMENTAL ONLINE MATERIAL
Supplemental material can be found online at http://www.mayoclinicproceedings.org.

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CORRECT ANSWERS: 1. a. 2. d. 3. b. 4. e. 5. c