

CLINICAL PRACTICE

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Acute Pericarditis

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A previously healthy 25-year-old man presents with pleuritic pain in the left side of the chest of 3 hours' duration, radiating to the left trapezius ridge and relieved by sitting forward. On physical examination, he appears anxious. His pulse is 104 beats per minute and regular, his blood pressure is 125/80 mm Hg without a paradoxical pulse, and his temperature is 37.8°C. A three-component friction rub is auscultated along the left sternal border. An electrocardiogram (ECG) reveals ST-segment elevations in multiple leads, which are consistent with acute pericarditis. How should this case be managed?

THE CLINICAL PROBLEM

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Acute pericarditis has numerous causes.^{1,2} However, in developed countries, roughly 80 to 90% of cases are idiopathic; that is, no specific cause is identified after routine evaluation, as discussed below. It is assumed that these cases are viral. The remaining 10 to 20% of cases are most commonly associated with post-cardiac injury syndromes, connective-tissue diseases (especially systemic lupus erythematosus), or cancer.^{2,3} Two rare, genetically determined autoinflammatory diseases — the tumor necrosis factor receptor-associated periodic syndrome (TRAPS) and familial Mediterranean fever — can target the pericardium and cause repeated bouts of inflammation.^{4,5} Because reperfusion therapy has markedly reduced the incidence of transmural myocardial infarction, post-myocardial infarction pericarditis, both early (i.e., 2 to 4 days after myocardial infarction) and late (also called Dressler's syndrome), has become unusual. Occasionally, however, patients present with symptomatic pericarditis after a clinically silent myocardial infarction.

The incidence of acute pericarditis is difficult to quantify, since mild cases may resolve without being diagnosed. Acute pericarditis is diagnosed in approximately 5% of patients in emergency departments who have nonischemic chest pain.^{3,6} There is a predominance of cases among men; in a recent large cohort study,⁷ men accounted for almost two thirds of patients hospitalized with acute pericarditis. In this study, the in-hospital mortality rate was 1.1%. As many as one third of cases of idiopathic pericarditis are associated with myocarditis, which is manifested as elevated biomarkers of myocardial injury, such as troponin I.^{3,8} Left-ventricular dysfunction is uncommon, and clinical heart failure and arrhythmias at the time of presentation are rare in patients with myocarditis.^{8,9} The long-term prognosis for patients who have idiopathic pericarditis with associated myocarditis is excellent.^{8,9}

Data from the recent randomized clinical trial Investigation on Colchicine for Acute Pericarditis (ICAP)¹⁰ indicate that pericardial effusions are present in about two thirds of patients with acute pericarditis. The vast majority of these effusions are small and of no concern.^{1-3,10} Large effusions (>20 mm in width as determined by means of echocardiography) are present in around 3% of cases.¹⁰ Large effusions

KEY CLINICAL POINTS

ACUTE PERICARDITIS

- The diagnosis of acute pericarditis requires at least two of the following symptoms or signs to be present: typical chest pain, pericardial friction rub, typical electrocardiographic changes, and pericardial effusion.
- In developed countries, 80 to 90% of cases are idiopathic and presumed to be viral.
- Evaluation includes a medical history and laboratory tests to help determine whether a specific cause is present, a chest radiograph, and an echocardiogram to determine whether there is an effusion.
- In response to treatment with a combination of a nonsteroidal antiinflammatory drug (NSAID) and colchicine, 70 to 90% of cases resolve completely; treatment with glucocorticoids should be avoided, if possible, because they increase the risk of recurrence.
- Patients with recurrent pericarditis should be treated with repeated courses of an NSAID and colchicine; if treatment with glucocorticoids cannot be avoided, moderate initial doses followed by gradual tapering provide the best outcomes.

are much more common in patients in whom a specific cause of pericarditis is identified than in those with idiopathic pericarditis.^{2,3} An effusion causing cardiac tamponade is the most important complication of acute pericarditis. Patients who present with acute pericarditis complicated by an effusion occasionally have effusive constrictive pericarditis, or this condition subsequently develops¹¹; these patients also typically have an identifiable cause of their pericarditis.

In 70 to 90% of patients, acute idiopathic pericarditis is self-limited, responds promptly to initial treatment (outlined below), and completely resolves.^{2,3,10,12} In a small number of patients, probably less than 5%, the condition does not respond satisfactorily to initial treatment, and in 10 to 30% of patients, recurrences develop after a satisfactory initial response.^{2,3,10,12} Most patients have only one or two recurrences, but a small fraction (probably less than 5% of the total population with acute pericarditis) have multiple recurrences with considerable disability. Ultimately, recurrences cease in the majority of cases.¹³

STRATEGIES AND EVIDENCE

EVALUATION

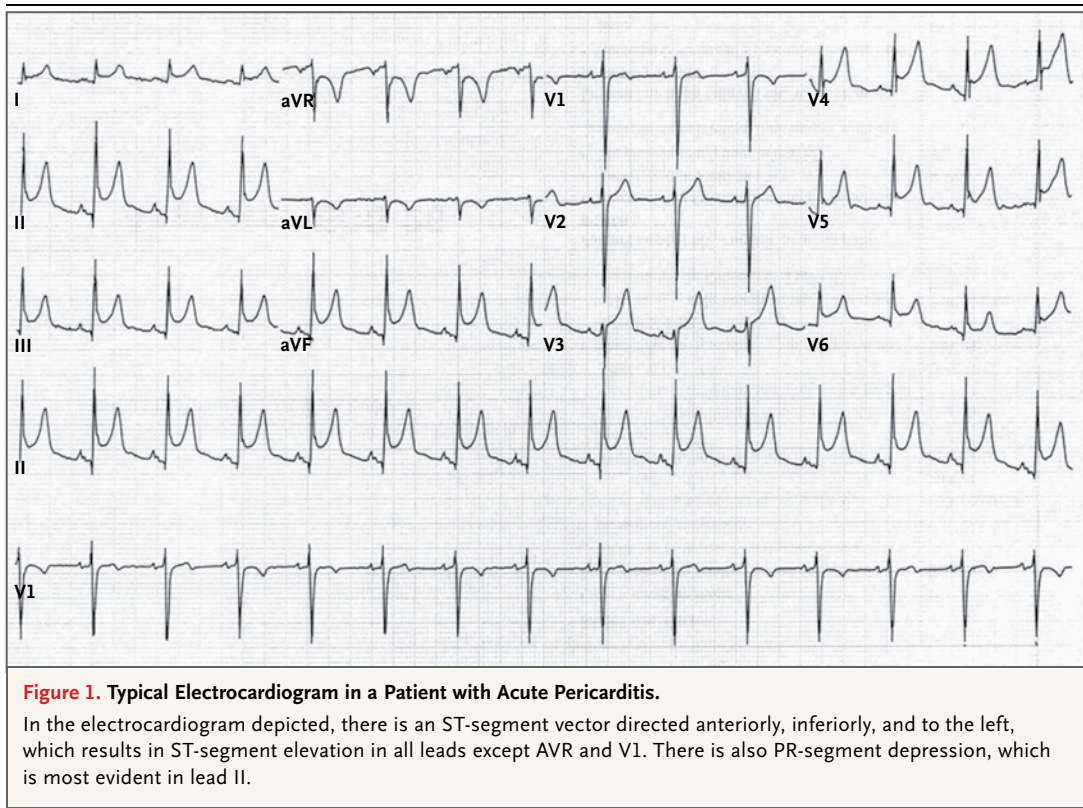
The diagnosis of acute pericarditis is established when a patient has at least two of the following symptoms or signs: chest pain consistent with pericarditis, pericardial friction rub, typical ECG changes, or a pericardial effusion of more than trivial size.² Since chest pain is the presenting symptom in virtually all patients for whom a di-

agnosis of pericarditis would be considered, as a practical matter, confirmation requires one additional criterion.

Although the differential diagnosis of chest pain is extensive, certain features point strongly to pericarditis, especially pleuritic pain that is relieved by sitting forward^{1,2} and that radiates to the trapezius ridge¹ (the latter feature is virtually pathognomonic). Many patients have premonitory symptoms suggestive of a viral illness, and an abrupt onset is not unusual. Sinus tachycardia and low-grade fever are also common. However, a temperature above 38.5°C suggests that a specific cause is present.¹⁴ Since pleuritic chest pain has many possible causes, pericarditis should be diagnosed with caution in the absence of other clinical criteria. Because the rub and ECG findings may be transient, frequent auscultation and ECG recordings can be helpful in establishing the diagnosis.

Cardiac tamponade is suspected if the jugular venous pressure is elevated, heart sounds are muffled, or the patient has hypotension (Beck's triad) or a paradoxical pulse. A large effusion usually enlarges the cardiac silhouette on a chest radiograph. However, a smaller but rapidly accumulating effusion can cause tamponade without enlarging the silhouette, which underscores the importance of echocardiography in patients with acute pericarditis even if the silhouette is normal.¹

Occasionally, ST-segment elevation is present in a more limited lead set than is shown in the classic example in Figure 1, which makes the distinction between pericarditis and ST-segment-eleva-

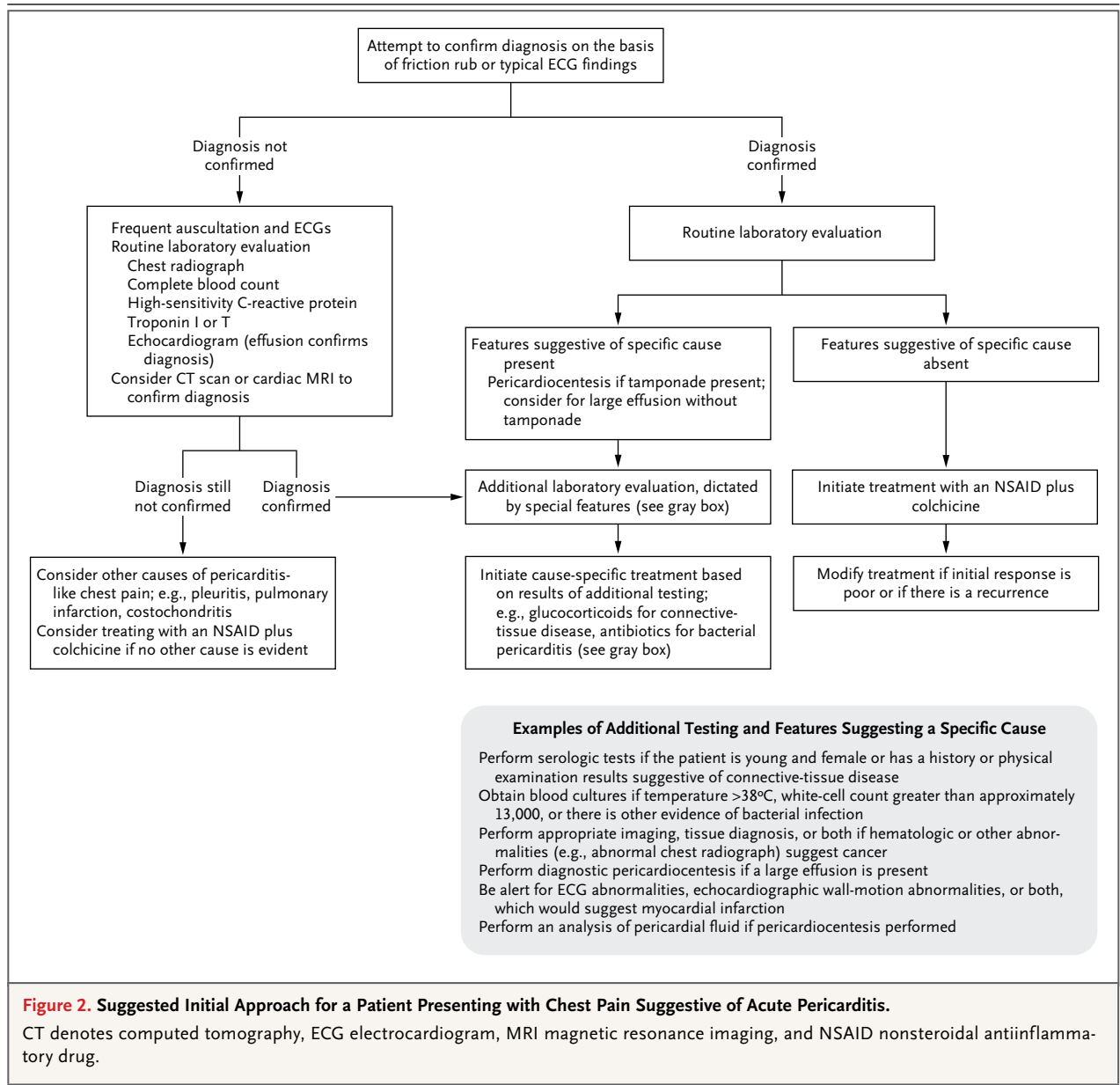


tion myocardial infarction more difficult; in some cases, PR-segment depression is the only ECG finding.¹⁻³ Early repolarization can also be confused with pericarditis. In rare cases, coronary angiography may be required to distinguish pericarditis from myocardial infarction. The other causes of chest pain that are most likely to be confused with acute pericarditis are pleuritis with or without associated pneumonia (which coexists with pericarditis in as many as one third of cases¹⁵), costochondritis, gastroesophageal reflux, pulmonary embolism or infarction, and herpes zoster before the appearance of vesicles.

A brief outline of a suggested approach to a patient presenting with chest pain suggestive of acute pericarditis is shown in Figure 2.^{2,3,16} The approach depends in part on whether the diagnosis can be confirmed on the basis of auscultation of a friction rub, typical ECG findings, or detection of a pericardial effusion. If the diagnosis is confirmed, further diagnostic evaluation should be performed to determine whether an identifiable cause is present and to rule out a potentially dangerous effusion. Appropriate tests include a complete blood count with a differential count, a

high-sensitivity test of C-reactive protein, measurements of troponin I or T and serum creatinine, and liver-function tests. In uncomplicated, acute idiopathic pericarditis, the white-cell count is typically modestly elevated. A white-cell count greater than about 13,000 per cubic millimeter suggests a specific cause (e.g., a bacterial infection). Anemia is not ordinarily present in patients with idiopathic pericarditis; its presence suggests an underlying disorder (e.g., connective-tissue disease or cancer) that can involve the pericardium. The high-sensitivity test of C-reactive protein shows an elevated level in about 75% of cases, which usually normalizes within 1 to 2 weeks.¹⁷ A chest radiograph should always be obtained, and findings should be normal unless there is a large pericardial effusion or an associated pulmonary disorder. In addition to changes consistent with pericarditis, the ECG may reveal evidence of a previous, silent myocardial infarction.

An echocardiogram is routinely indicated for patients with suspected or confirmed pericarditis. The most important rationale is detection of a pericardial effusion, which as noted above, can cause or threaten to cause cardiac tamponade



without enlarging the cardiac silhouette on a chest radiograph.

If the diagnosis of pericarditis is confirmed and there is no reason to suspect a specific cause, further testing is unnecessary. If a specific cause is suspected on the basis of the medical history, the results of physical examination, or laboratory findings that suggest a causative disorder (e.g., cancer or connective-tissue disease), appropriate additional evaluation is indicated (Fig. 2).

Cases in which pericarditis is suspected but difficult to confirm can be challenging. Although

not routinely indicated, cardiac magnetic resonance imaging (MRI) or computed tomographic scanning can be helpful, because pericardial thickening, enhanced pericardial gadolinium uptake on MRI, or both support the diagnosis.¹⁸ An elevated C-reactive protein level on high-sensitivity testing, although nonspecific, is also supportive. If the history is convincing and other entities that can cause pleuritic chest pain are ruled out, it is reasonable to provide treatment for pericarditis in the absence of confirmatory findings.^{2,3}

TREATMENT

Patients with cardiac tamponade should undergo urgent therapeutic pericardiocentesis. Pericardiocentesis should also be considered for patients with large effusions without tamponade. In the rare cases in which patients have myocarditis and heart failure,^{8,9} these patients should be hospitalized for observation and institution of appropriate therapy.

Nonsteroidal antiinflammatory drugs (NSAIDs) have long been the mainstay of the initial treatment of acute pericarditis.^{1-3,16,19,20} The most commonly used agents are ibuprofen (600 to 800 mg every 6 to 8 hours), indomethacin (25 to 50 mg every 8 hours), and aspirin (2 to 4 g daily in divided doses). Ibuprofen has been preferred in North America, whereas aspirin tends to be favored in Europe. Patients receiving these drugs should also receive a proton-pump inhibitor for gastric protection.^{2,3}

On the basis of observational data from a relatively small number of patients with recurrent pericarditis,²¹ the European Society of Cardiology (ESC) concluded in its 2004 guidelines² that there was sufficient evidence to recommend colchicine combined with an NSAID for initial treatment of a first bout of pericarditis. More recently, evidence from the ICAP randomized clinical trial,¹⁰ involving patients with a first episode of pericarditis, strongly supported this recommendation. In the ICAP trial, patients were treated with an antiinflammatory agent (most commonly aspirin) and were randomly assigned to receive either colchicine (0.5 mg twice daily in patients with a body weight of >70 kg or 0.5 mg daily in patients with a body weight of ≤70 kg, for 3 months) or placebo. To minimize gastrointestinal side effects, a loading dose of colchicine was not used. Treatment with colchicine, as compared with placebo, resulted in a significantly lower rate of persistent or recurrent pericarditis (17% vs. 38%) and a lower rate of persistent symptoms at 72 hours (19% vs. 40%). Although about 10% of patients were withdrawn from the study because of gastrointestinal side effects, the rates of drug discontinuation were similar in the colchicine and placebo groups. The efficacy of colchicine is thought to result from an antiinflammatory effect caused by blockade of microtubule assembly in white cells.²⁰

Aspirin is the preferred NSAID for patients with symptomatic pericarditis that occurs during the early post-myocardial infarction period and, in

combination with colchicine, for most other patients who require concomitant antiplatelet therapy.^{2,3,19,21} In patients with pericarditis as a manifestation of connective-tissue or other immune-mediated disorders, glucocorticoids are generally the preferred initial treatment.^{2,3,20}

Most patients have a good initial response to an NSAID and colchicine and are free or largely free of symptoms within a few days. Patients without an effusion or with only a small effusion who can be expected to adhere to the NSAID–colchicine regimen and who have a prompt response need not be admitted to a hospital. A study of the use of a triage protocol for 300 patients with acute pericarditis showed that for low-risk patients (i.e., those with a subacute onset who did not have fever, immunosuppression, trauma, myopericarditis, a large pericardial effusion, or cardiac tamponade and were not receiving anticoagulant therapy), who accounted for 85% of patients overall, the condition could safely be managed on an outpatient basis; only 13% of these patients required subsequent admission (for aspirin failure), and there were no major complications.¹⁴

The optimal duration of treatment is uncertain. For colchicine, a 3-month course is reasonable on the basis of results from the ICAP trial. The usual duration of NSAID treatment, supported by expert opinion,^{2,3,14,16,19} is 1 to 2 weeks, with the actual duration driven by clinical response. Some physicians favor gradual tapering rather than abrupt discontinuation, but there is no evidence in support of this. In the ICAP trial,¹⁰ the NSAID treatment strategy was not prespecified; most patients received NSAID treatment for 7 to 10 days, followed by tapering. It has been proposed that normalization of the C-reactive protein level on high-sensitivity testing (if elevated initially) be used to guide the duration of NSAID therapy,¹⁷ although data are lacking to support this strategy.

A poor initial response to an NSAID and colchicine — defined as continued chest pain necessitating treatment with analgesic agents, fever, or worsening effusion despite at least 1 week of treatment^{2,3} — is unusual but poses a difficult management problem; it also increases the possibility of identifying a specific cause. For patients with a poor response, the ESC guidelines² (which are based on clinical experience) support the addition of glucocorticoids. If the adverse-effect profile is acceptable, treatment with the NSAID should be continued.^{16,21} Observational data indicate a

high rate of symptom relief in patients treated with glucocorticoids but also an increased recurrence rate, as compared with patients treated with other antiinflammatory agents.^{3,20,21} Moreover, glucocorticoids appear to blunt the beneficial effects of colchicine in reducing recurrences.²² These observations, as well as the other adverse effects of glucocorticoids, argue against their use unless absolutely necessary. Glucocorticoid regimens in which a high initial dose is followed by rapid tapering appear to be especially problematic with respect to recurrences.^{15,23} If glucocorticoid treatment cannot be avoided, clinical experience suggests that it is preferable to use moderate doses (0.2 to 0.5 mg of prednisone per kilogram of body weight daily) for several weeks and then begin gradual tapering (e.g., a dose reduction every 1 to 2 weeks over a period of 2 to 4 months), assuming the symptoms are improved.^{15,20,23} Continuation of treatment with an NSAID and colchicine for a period after glucocorticoid discontinuation is also recommended, although data are lacking to guide the duration of continued treatment in this situation.

RECURRENT PERICARDITIS

The risk of recurrence is higher for women and for patients who do not have a response to initial treatment with NSAIDs.²³ It has been speculated that some patients with recurrent pericarditis have an autoinflammatory disorder related to TRAPS.^{12,21,24}

Treatment of a recurrence should begin with prompt reinstitution of NSAID therapy at the same dosage as for the initial episode.^{2,3} If colchicine treatment was not administered initially, it should be given for a recurrence, because there is evidence from randomized clinical trials that it reduces the risk of future recurrences after one or multiple recurrences.^{12,21,24} In a randomized trial involving patients with a first recurrence,¹² treatment with colchicine (1 to 2 mg on the first day, followed by 0.5 to 1.0 mg daily for 6 months) in addition to aspirin (or prednisone) resulted in about half the risk of future recurrence, as compared with treatment with aspirin (or prednisone) alone (24% vs. 51% over a period of 18 months).

In many cases, patients have a good response to reinstitution of NSAID treatment and should be encouraged to restart treatment with an NSAID in the future at the first symptom of a recurrence. Recurrences can be managed in this manner as

long as NSAIDs continue to be effective, with an acceptable adverse-effect profile, and as long as symptoms are not disabling.

In unusual cases involving patients who have frequent, disabling recurrences or who have a poor response to reinstitution of NSAID therapy, glucocorticoids are commonly used. The regimen should be the same as that for patients with a poor response to initial treatment. For the reasons stated above, treatment with glucocorticoids should be avoided if possible. Experience with other immunomodulatory agents in refractory recurrent pericarditis is very limited, but studies involving small numbers of patients have shown improvements after treatment with immune globulins,²⁵ anti-tumor necrosis factor α antibody,²⁶ azathioprine,²⁷ or anakinra,²⁸ an interleukin-1 β antagonist.

Although recurrent pericarditis can be very disabling, patients can be reassured that, in the absence of an identified underlying cause, serious late complications (e.g., constrictive pericarditis) are extremely rare, and most cases eventually resolve.^{13,15} Pericardiectomy has occasionally been used to treat refractory recurrent pericarditis. Although studies of case series have suggested a clinical benefit,^{29,30} pericardiectomy is not consistently effective, perhaps because visceral pericardium remains after the procedure, along with remnants of parietal pericardium.

AREAS OF UNCERTAINTY

Little is known about the pathophysiological aspects of recurrent pericarditis. Some patients do not have evidence of pericardial inflammation during recurrences, and it is unclear whether patients with recurrences have an active viral infection or an immunologic basis for the syndrome. A report that HLA allele patterns are associated with recurrent pericarditis³¹ may support the latter possibility. Mechanistic studies involving these patients are needed.

Data from randomized clinical trials are lacking to guide the choice and duration of antiinflammatory treatment, to compare the effects of aspirin versus ibuprofen versus indomethacin as initial treatment, and to inform the use of glucocorticoids. There is also uncertainty regarding the role of high-sensitivity testing of C-reactive protein in guiding treatment responses. Finally, more data are needed to inform the role for novel forms of

immunomodulatory therapy in the treatment of patients with refractory recurrent pericarditis.

GUIDELINES

The 2004 ESC guidelines² remains the only formal guidance for the management of acute pericarditis. The recommendations in the present article are largely consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has chest pain consistent with pericarditis, a pericardial rub,

and ECG changes typical of acute pericarditis. If, on the basis of the evaluation outlined in Figure 2, he does not have clinical or laboratory features that suggest a specific, nonviral cause, no additional testing is warranted. On the basis of clinical experience with NSAIDs and data from randomized trials supporting the addition of colchicine, I recommend treatment with an NSAID — for example, 600 to 800 mg of ibuprofen every 6 to 8 hours for 10 to 14 days, with tapering based on clinical response — in conjunction with a proton-pump inhibitor, as well as treatment with colchicine for 3 months.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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