Case Presentation: A 56-year-old previously healthy man presented with 2 days of pleuritic left anterior chest pain, lessened by sitting forward. His examination was pertinent for low-grade fever (37.6°C), blood pressure 122/76 mm Hg without paradox, no jugular venous distension, clear lungs, and a 3-component pericardial friction rub. The ECG showed diffuse concave-upward ST-segment elevation and PR-segment depression in the inferior leads. The serum C-reactive protein level was 64 mg/L, and the cardiac troponin T was not elevated. Echocardiography showed normal left ventricular contractile function without wall motion abnormalities and no pericardial effusion. He was diagnosed with acute pericarditis, and the symptoms responded promptly to oral ibuprofen, continued for 2 weeks. Six weeks later, he redeveloped pleuritic chest pain and clinical and ECG findings identical to the initial presentation. His primary care physician asks for advice about appropriate therapy.

Background
Pericarditis accounts for 5% of emergency department visits for chest pain in the absence of myocardial infarction.1 In ~80% of cases in developed countries, the cause of pericarditis is either postviral or “idiopathic,” in that it cannot be attributed to a specific condition.2,3 Because these 2 etiologies are clinically equivalent, the term idiopathic pericarditis will refer to both in this Clinician Update. Even when managed effectively, many patients with acute pericarditis present with 1 or more repeated episodes, termed recurrent pericarditis.4

Acute Pericarditis Management
Treatment of idiopathic pericarditis has long been empirical, because until recently, there have been few therapeutic trials addressing this condition. The European Society of Cardiology published the only treatment guideline for pericarditis almost a decade ago, and many of the recommendations were based on opinion because of the lack of available study evidence.5

Most patients with idiopathic pericarditis experience self-limited symptoms that improve spontaneously within days to weeks. More rapid relief can be achieved with pharmacological intervention, and stable patients can be managed in the outpatient setting. Hospitalization is recommended when features suggest nonidiopathic causes or herald hemodynamic compromise, including fever >38°C (>100.4°F), the subacute development of symptoms (characteristic of tuberculosis, neoplastic disease, uremia, or collagen vascular disorders), hypotension, jugular venous distension, a large pericardial effusion, or echocardiographic features of impending tamponade (Figure).6,7 Patients who are immunocompromised or are undergoing therapy with anticoagulants should also be observed initially in the hospital.5

Pharmacological Treatment
Effective agents include nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and glucocorticoids. Concurrently, rest and avoidance of demanding physical activity help to minimize symptoms.

Nonsteroidal Anti-inflammatory Drugs
Aspirin and other NSAIDs are the first-line approach, based on clinical experience and observational reports.5,7 For example, in a 2004 study without a control group, outpatient therapy of uncomplicated pericarditis with aspirin relieved symptoms in 87% of 254 patients.5 Commonly used NSAID regimens are listed in the Table, with a recommended initial duration of 7 to 14 days, then treatment should be tapered until resolution of symptoms and improvement of acutely elevated serum inflammatory markers such as C-reactive protein and the erythrocyte
 sedimentation rate. Because high doses are often required, consideration should also be given to gastric protection therapy (eg, a proton pump inhibitor or misoprostol)3.

No single NSAID appears to be more effective than another in acute pericarditis, and in addition to oral agents, the parenteral NSAID ketorolac was shown to rapidly relieve symptoms in an uncontrolled trial.4 Aspirin is the preferred anti-inflammatory agent for patients with pericarditis after myocardial infarction because other NSAIDs have delayed infarct healing in animal models and are associated with an increased risk of future coronary events in this population.10

A rapid response to aspirin or other NSAID therapy predicts a favorable prognosis in acute pericarditis and an unlikely progression to complications such as pericardial constriction.5 However, if chest discomfort or fever persists >1 week, or a new or larger pericardial effusion develops during therapy, a cause of pericarditis other than postviral/idiopathic should be suspected. In the report of 254 patients with acute pericarditis treated as outpatients with aspirin, 61% of those with symptoms who did not respond by 7 days of therapy were ultimately found not to have idiopathic pericarditis. Forty-three percent were determined to have autoimmune conditions, and 18% had tuberculosis.5

### Colchicine

On the basis of its anti-inflammatory effectiveness in the serositis of familial Mediterranean fever, colchicine therapy for pericarditis was initially described in small observational reports >2 decades ago.11 Consensus opinion in the 2004 European Society of Cardiology guidelines listed colchicine as effective in recurrent pericarditis, and probably in acute pericarditis, for which it was assigned a class IIa indication.4 Subsequent prospective trials have provided additional evidence. In the open-label Colchicine in Acute Pericarditis (COPE) trial, 120 patients with a first episode of acute pericarditis were randomized to receive colchicine (0.5–1.0 mg daily for 3 months after 1–2 mg on the first day) plus aspirin (800 mg every 6–8 hours for 7–10 days, then tapered over 3–4 weeks) or aspirin alone.12 The rate of recurrent pericarditis over the subsequent 18 months was 32.3% in the aspirin group but only 10.7% in those who received colchicine plus aspirin (P=0.004). In addition, whereas 36.7% of patients in the aspirin group were still symptomatic at 72 hours after presentation, only 11.7% of those who also received colchicine remained symptomatic (P=0.003).

Long-term low-dose colchicine is well tolerated, requiring discontinuation only rarely, primarily for diarrhea.12 Uncommon serious side effects, occurring primarily in patients with chronic renal insufficiency, include hepatic toxicity and myelosuppression. It is now common practice to include colchicine, in combination with an NSAID, as initial management of acute idiopathic pericarditis (Table).

### Glucocorticoids

Steroid therapy has long been used to treat pericarditis because it induces prompt symptomatic relief; however, glucocorticoids should not be used as primary therapy in uncomplicated acute idiopathic pericarditis because of a high rate of relapse when the steroid is tapered or stopped.4,12,13 Glucocorticoids also appear to blunt the efficacy of colchicine in preventing recurrences.14 As a result, and owing to the side effects associated with long-term steroid therapy, glucocorticoids should only be prescribed to patients with idiopathic pericarditis who are refractory to treatment with, or intolerant of, an NSAID plus colchicine.4

When used, the prednisone dosage recommended in the 2004 European Society of Cardiology guidelines was a relatively high 1.0 mg·kg\(^{-1}\)·d\(^{-1}\) for 2 weeks with rapid tapering. A lower dosage (0.25–0.50 mg·kg\(^{-1}\)·d\(^{-1}\)) for 2 to 4 weeks, followed by slow tapering (Table) is effective and is associated with fewer relapses than the higher dosage.15

### Recurrent Pericarditis Management

One or more recurrences arise in 15% to 30% of patients after an initial episode of acute pericarditis.2 These attacks can

<table>
<thead>
<tr>
<th>Table. Pharmacological Treatment of Idiopathic Pericarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>Aspirin</td>
</tr>
<tr>
<td>Ibuprofen</td>
</tr>
<tr>
<td>Indomethacin</td>
</tr>
<tr>
<td>Ketorolac</td>
</tr>
<tr>
<td>Colchicine</td>
</tr>
<tr>
<td>Prednisone</td>
</tr>
<tr>
<td>At dose of:</td>
</tr>
<tr>
<td>25–50 mg daily</td>
</tr>
<tr>
<td>15–25 mg daily</td>
</tr>
<tr>
<td>&gt;15 mg daily</td>
</tr>
</tbody>
</table>

IM indicates intramuscular administration; IV, intravenous administration; and PO, by mouth.

*Reduced dosage recommended for patients with advanced renal dysfunction or concurrent therapy with moderate to strong inhibitors of CYP3A4 (eg, protease inhibitors, ketoconazole, fluconazole, erythromycin, diltiazem, verapamil) or P-glycoprotein inhibitors (eg, cyclosporine).

†As recommended by Imazio et al.2
repeat over extended periods of time and may lead to substantial disability. A first recurrence typically presents within 18 months, and findings are similar to the initial episode, including pleuritic chest pain, diffuse ST-segment elevations, a pericardial friction rub, and elevated serum markers of inflammation.16

Pharmacological Treatment

Nonsteroidal Anti-inflammatory Drugs
In the absence of prospective trial evidence, aspirin or another NSAID should form the foundation of therapy for recurrences (Table).4 However, in contrast to the brief course of NSAID generally prescribed for an initial episode, a gradual tapering of the drug over 2 to 4 weeks after symptoms improve is recommended.16

Colchicine
Use of colchicine in the COPE trial was associated with fewer initial pericarditis recurrences.12 Additionally, the Colchicine for Recurrent Pericarditis (CORE) trial randomized 84 patients who had already had a first recurrence to aspirin or aspirin plus colchicine.16 Compared with aspirin alone, the combination reduced the rate of additional recurrences by 50%.

Most recently, the double-blinded Colchicine for Recurrent Pericarditis (CORP) trial randomized 120 patients with a first recurrence to colchicine or placebo, in addition to aspirin or another NSAID.17 The rate of subsequent recurrence was 24% in those randomized to colchicine compared with 55% in the placebo group. In addition, the mean number of episodes was reduced and the time to next recurrence was lengthened. The duration of colchicine therapy in the CORE and CORP trials for recurrent pericarditis was 6 months.

Glucocorticoids
Symptoms of pericarditis recurrence respond promptly to glucocorticoid therapy.1 However, when administered in this situation, slow tapering and a prolonged course may be required to prevent recrudescent symptoms, with the potential for long-term steroid-associated side effects. Furthermore, the risk of additional recurrences of pericarditis is augmented by steroid use.12,14,16 Therefore, the consensus is to initially treat recurrent episodes of pericarditis with an NSAID plus colchicine and to prescribe glucocorticoids only for refractory cases.

Patients sometimes present with chest discomfort reminiscent of prior pericarditis, which is interpreted as a recurrence, even in the absence of objective findings (no pericardial rub, ECG or echocardiographic abnormalities, or elevation of serum inflammatory markers). Although a trial of an NSAID plus colchicine may be reasonable in this situation, glucocorticoids should certainly be avoided.18

Imazio and colleagues15 compared 2 steroid dosage intensities in recurrent pericarditis: Prednisone 0.2 to 0.5 mg·kg⁻¹·d⁻¹ versus the higher commonly used dose of 1.0 mg·kg⁻¹·d⁻¹ for 4 weeks, followed by a slow taper. The lower-dose regimen was effective, whereas the higher dosage was associated with more side effects and a greater number of subsequent pericarditis recurrences and hospitalizations. Thus, a now common approach to the use of steroids in patients with recurrent pericarditis whose symptoms are refractory to an NSAID plus colchicine is the lower-dose prednisone regimen listed in the Table. With prolonged corticosteroid
use, osteoporosis prevention (eg, calcium, vitamin D, and bisphosphonates) should be considered.

A common cause of referral to specialized pericardial centers is the inability to taper glucocorticoid therapy below a certain dosage (typically ≥15 mg of prednisone daily) without reemergence of symptoms, despite concurrent NSAID plus colchicine treatment. An often effective strategy in this circumstance is to resume the lowest prior steroid dosage that had controlled symptoms, and then taper it by only 1 to 2 mg every 2 to 4 weeks.19

Other Considerations
For refractory pericarditis despite NSAID, colchicine, and glucocorticoid therapies, improved symptoms have been reported in small numbers of patients with the use of immunosuppressive agents (azathioprine or methotrexate), intravenous immunoglobulin, and the interleukin-1β receptor antagonist anakinra.2 Finally, pericardioectomy can be undertaken for symptomatic relief in cases of continuously relapsing pericarditis.3 Results have been variable, with some patients experiencing complete remission but others continuing to be plagued with ongoing symptoms after surgical intervention. The best outcomes have been reported when complete resection of the pericardium is undertaken.20

Case Presentation
(Continued)

The patient’s recurrent pericarditis was treated with ibuprofen 600 mg 3 times daily plus colchicine 0.6 mg twice daily. Ibuprofen was tapered off after 3 weeks, and the colchicine was continued for 6 months. After 1 additional year of follow-up, he has had no further symptoms of pericarditis.

Summary
Appropriate therapy for acute idiopathic pericarditis is an NSAID for ≥2 weeks, and it is also reasonable to prescribe colchicine for up to 3 months (the duration used in clinical trials), especially to reduce the rate of recurrence. For initially refractory symptoms, the parenteral NSAID ketorolac may be beneficial. For recurrent episodes of pericarditis, treatment with an NSAID plus colchicine is recommended, but for a more prolonged course. During NSAID treatment, concurrent gastric protection therapy should be considered. Only for truly refractory cases should glucocorticoid therapy be used.

Disclosures
None.

References

Key Words: colchicine • drug therapy • pericarditis
Treatment of Acute and Recurrent Idiopathic Pericarditis
Leonard S. Lilly

Circulation. 2013;127:1723-1726
doi: 10.1161/CIRCULATIONAHA.111.066365
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/127/16/1723

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at: http://circ.ahajournals.org/subscriptions/