Review

Evaluation and Treatment of Pericarditis
A Systematic Review

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IMPORTANCE Pericarditis is the most common form of pericardial disease and a relatively common cause of chest pain.

OBJECTIVE To summarize published evidence on the causes, diagnosis, therapy, prevention, and prognosis of pericarditis.

EVIDENCE REVIEW A literature search of BioMedCentral, Google Scholar, MEDLINE, Scopus, and the Cochrane Database of Systematic Reviews was performed for human studies without language restriction from January 1, 1990, to August 31, 2015. After literature review and selection of meta-analyses, randomized clinical trials, and large observational studies, 30 studies (5 meta-analyses, 10 randomized clinical trials, and 16 cohort studies) with 7569 adult patients were selected for inclusion.

FINDINGS The etiology of pericarditis may be infectious (eg, viral and bacterial) or noninfectious (eg, systemic inflammatory diseases, cancer, and post–cardiac injury syndromes). Tuberculosis is a major cause of pericarditis in developing countries but accounts for less than 5% of cases in developed countries, where idiopathic, presumed viral causes are responsible for 80% to 90% of cases. The diagnosis is based on clinical criteria including chest pain, a pericardial rub, electrocardiographic changes, and pericardial effusion. Certain features at presentation (temperature >38°C [>100.4°F], subacute course, large effusion or tamponade, and failure of nonsteroidal anti-inflammatory drug [NSAID] treatment) indicate a poorer prognosis and identify patients requiring hospital admission. The most common treatment for idiopathic and viral pericarditis in North America and Europe is NSAID therapy. Adjunctive colchicine can ameliorate the initial episode and is associated with approximately 50% lower recurrence rates. Corticosteroids are a second-line therapy for those who do not respond, are intolerant, or have contraindications to NSAIDs and colchicine. Recurrences may occur in 30% of patients without preventive therapy.

CONCLUSIONS AND RELEVANCE Pericarditis is the most common form of pericardial disease worldwide and may recur in as many as one-third of patients who present with idiopathic or viral pericarditis. Appropriate triage and treatment with NSAIDs may reduce readmission rates for pericarditis. Treatment with colchicine can reduce recurrence rates.

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Pericarditis is the most common form of pericardial disease worldwide.[1-10] Pericarditis usually affects young and middle-aged individuals and frequently recurs.[1,2] In a prospective, observational cohort study involving 2 general hospitals from an Italian urban area of 220 000 inhabitants, an incidence of 27.7 cases per 100 000 population per year was reported.[3] Data from a Finnish national registry[4] demonstrated a standardized incidence rate of hospitalizations for acute pericarditis of 3.32 per 100 000 person-years, with a higher proportion of men. Overall, pericarditis accounts for 0.2% of all hospital cardiovascular admissions[4] and is diagnosed in approximately 5% of patients with nonischemic chest pain in emergency departments in North America and Western Europe.[5,6] In developed countries, the in-hospital mortality rate is approximately 1.1%. Prognosis is determined in part by patient age and etiology.[4,7]

Pericarditis may be a manifestation of underlying systemic disease or a primary process unrelated to systemic disease (**Box 1**).[8-10] Limited epidemiological data are available, and the exact incidence is difficult to estimate because mild cases may resolve without a diagnosis. However, failure to recognize and treat pericarditis may prolong the disease course and increase recurrences.[11,12]

Evidence for pericarditis therapy has advanced in the last 10 years. The first randomized clinical trials (RCTs)[1,2,13-18] and observational studies[7,19] have likely contributed to improved outcomes

Box 1. Etiology of Pericarditis[a]

Infectious Causes

Viral (common): Enteroviruses (especially Coxsackieviruses, echoviruses); herpesviruses (especially Epstein-Barr virus, cytomegalovirus, human herpesvirus 6); adenoviruses (especially in children); parvovirus B19

Bacterial: *Mycobacterium tuberculosis* (common; other rare), *Coxiella burnetii*, *Borrelia burgdorferi*; rarely other microorganisms, usually as purulent pericarditis[b]

Fungal (rare): *Histoplasma* species (more likely in immunocompetent patients); *Aspergillus*, *Blastomyces*, and *Candida* species (more likely in immunocompromised host)

Parasitic (rare): *Echinococcus* and *Toxoplasma* species

Noninfectious Causes

Autoimmune and autoinflammatory (common)

- Systemic autoimmune (especially systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, scleroderma)
- Systemic vasculitides (especially eosinophilic granulomatosis with polyangiitis or allergic granulomatosis, previously named Churg-Strauss syndrome, Horton disease, Takayasu disease, Behçet syndrome)
- Autoinflammatory diseases (familial Mediterranean fever, tumor necrosis factor receptor–associated periodic syndrome)
- Other (sarcoidosis, inflammatory bowel diseases)

Neoplastic

- Primary tumors (rare; pericardial mesothelioma)
- Secondary metastatic tumors (common; lung and breast cancer, lymphoma)

Metabolic (common): Uremia, myxedema, anorexia nervosa, other rare

Traumatic and iatrogenic (common)

- Early onset: Direct injury (penetrating thoracic injury, esophageal perforation); indirect injury (nonpenetrating thoracic injury, radiation injury)
- Delayed onset: Pericardial injury syndromes (post–myocardial infarction syndrome, postpericardiotomy syndrome); posttraumatic, including after iatrogenic trauma (eg, coronary percutaneous intervention, pacemaker lead insertion, and radiofrequency ablation)

Drug related (rare)

- Lupus-like syndrome (procainamide, hydralazine, methyldopa, isoniazid, phenytoin)
- Hypersensitivity pericarditis with eosinophilia (eg, penicillins)
- Pericardial and myocardial involment (eg, antineoplastic drugs: doxorubicin, daunorubicin, cytosine arabinoside, fluorouracil, cyclophosphamide)

[a] The pericardium may be affected by all categories of diseases, including infectious, autoimmune, neoplastic, iatrogenic, traumatic, and metabolic.

[b] *Pneumococcus*, *Meningococcus*, *Gonococcus*, *Streptococcus*, *Staphylococcus*, *Haemophilus*, *Chlamydia*, *Mycoplasma*, *Legionella*, *Leptospira*, and *Listeria* species and *Providencia stuartii*.

and reduced recurrences[1,2,7,13-23] Well-defined criteria for diagnosis, integrated imaging, and diagnostic workup have been recently proposed.[20,21] This review summarizes current evidence regarding the causes, diagnosis, therapy, prevention, and prognosis of pericarditis.

Methods

A literature search of BioMedCentral, Google Scholar, MEDLINE, Scopus, and the Cochrane Database of Systematic Reviews was performed for human studies without language restriction from January 1, 1990, to August 31, 2015, using the search terms *pericarditis*, *diagnosis*, *drug therapy*, and *prognosis*. Potentially relevant articles were reviewed to exclude duplicates and to ensure they included patients with objectively confirmed pericarditis. The review included meta-analyses, clinical trials, and large observational studies with at least 100 patients (eFigure 1 in the Supplement). Available levels of evidence for each diagnostic and therapeutic intervention were reviewed and classified according to American Heart Association/American College of Cardiology guidelines (eTable 1 in the Supplement).

Data have been prioritized to emphasize the highest quality of evidence, defined as RCTs and meta-analyses. Findings of the present analysis were compared with current guidelines and consensus statements.

Results

Thirty-one studies (5 meta-analyses, 10 RCTs, and 16 cohort studies) with 7569 adult patients were selected for inclusion (eFigure 1 in the Supplement).

Pathophysiology

The etiology of pericarditis may be categorized as infectious or noninfectious (**Table 1**). The prompt recognition of a likely cause of pericarditis may be critical. In developing countries with a high prevalence of tuberculosis, tuberculosis accounts for about 70% of pericarditis diagnoses and has a high mortality: about 25% at 6 months in the absence of human immunodeficiency virus (HIV) infection and approximately 40% in those with associated HIV infection.[8,9]

Tuberculous pericarditis is much less common in developed countries, accounting for less than 5% of all cases.[19,23-26] Immigration may increase these cases in developed countries.[9]

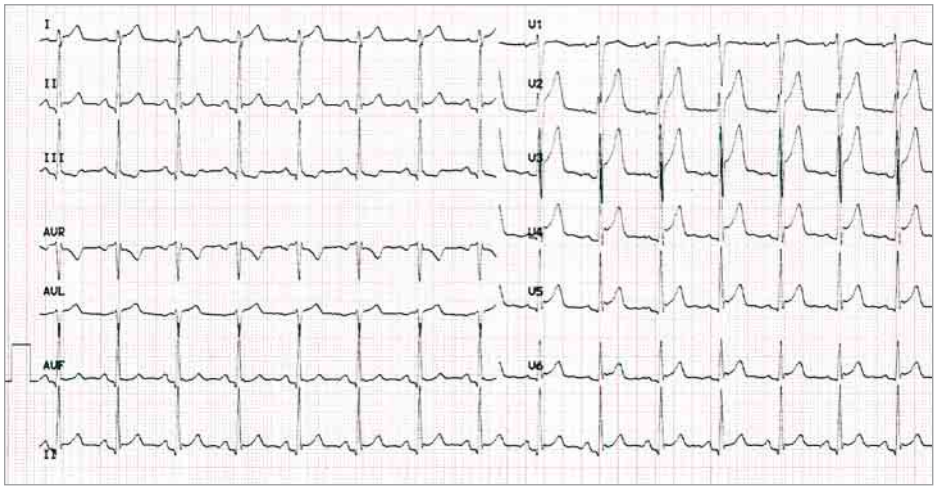
In Western Europe and North America, about 80% to 90% of cases are labeled "idiopathic" after a diagnostic workup, and most are presumed to be viral.[5,6] The remaining cases with an identified etiology include, in unselected populations, neoplastic pericardial disease (5%-10%), systemic inflammatory diseases and pericardial injury syndromes (2%-7%), tuberculous pericarditis (about 4%), and purulent pericarditis (<1%) (Table 1).[19,24,25] In a recent French study consisting of patients hospitalized with acute pericarditis admitted from the emergency department or from cardiology and cardiac surgery departments, the etiologies of acute pericarditis were idiopathic in 516 of 933 (55%), autoimmune or post–cardiac injury syndromes in 222 of 933 (24%), neoplastic in 83 of 933 (9%), bacterial in 29 of 933 (3.1%), and tuberculosis in only 5 cases (0.5%). This study suggests that hospitalized patients are usually more complicated cases with a higher risk of a nonidiopathic etiology.[26] Moreover, in developed countries, the aging of the population, with increased use of cardiovascular interventions (eg, percutaneous coronary intervention, arrhythmia ablation, device implantation), has increased the possible risk of "pericardial complications," with even minor intra-

Table 1. Reported Etiology of Pericarditis in Published Series

Etiology	Reported Frequency as Percentage of Reported Cases of Pericarditis
Idiopathic[5,6,9,19,23-26]	15% (Africa) to 80%-90% (Europe and United States)
Infectious	
Viral (eg, Coxsackievirus, Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, parvovirus B19)[5,6,9,19,23-26]	Largely unknown (30%-50% in Marburg, Germany experience)
Bacterial[9,19,23-26]	
Tuberculosis	1%-4% (Italy, Spain, France), up to 70% (Africa)
Purulent	<1% (Europe) to 2%-3% (mainly Africa); rare (largely unknown)
Other infectious causes[9,19,23-26]	
Noninfectious	
Neoplastic etiology[9,19,23-27]	5%-9% to 35% (in tertiary European referral centers)
Autoimmune[9,19,23-25,a]	2%-24%
Other	Rare (largely unknown)

[a] Systemic inflammatory disease and pericardial injury syndromes.

Figure 1. Widespread ST-Segment Elevation and PR-Segment Depression in a 12-Lead Electrocardiogram From a Patient With Acute Pericarditis



Widespread ST-segment elevation, considered characteristic of pericarditis, can be found in no more than 60% of patients with acute pericarditis and is more common in younger male patients, especially in association with myocarditis.[3,51] PR depression is especially evident in inferior leads (II, aVF, III) and precordial leads (V2-V6). Electrocardiogram (ECG) findings may be affected by timing in the course of the disease and by treatment. Early in the disease, ECG changes may include ST-segment elevation. Later in the disease and in chronic pericarditis, the ECG may be normal or have negative T waves, reflecting an ECG in evolution. In patients with a rapid response to medical therapy and in mild acute pericarditis, the ECG may be normal. Thus, a normal ECG does not exclude pericarditis.

pericardial bleeding potentially causing pericarditis (pericardial injury syndromes).[12,26]

Clinical Presentation

The classic and most common presentation of patients with pericarditis is chest pain. The chest pain is typically sharp and pleuritic, improved by sitting up and leaning forward. Additional signs in acute pericarditis include (1) pericardial friction rubs, reported in about one-third of cases with acute pericarditis and due to increased friction of inflamed pericardial layers; (2) a "typical electrocardiogram" with widespread ST-segment elevation, reported in no more than 60% of cases (**Figure 1**); and (3) pericardial effusion (usually mild), detected in about 60% of patients (**Figure 2**).[1,2] Specific features at presentation (temperature >38°C [>100.4°F], subacute course, large effusion or tamponade, and failure of nonsteroidal anti-inflammatory drug [NSAID] therapy) are useful indicators of a poor prognosis. These characteristics also identify patients requiring hospital admission, thus allowing triage of patients with pericarditis, since the presence of 1 or more of these features indicates the need for hospitalization (eFigure 2 in the Supplement).[19]

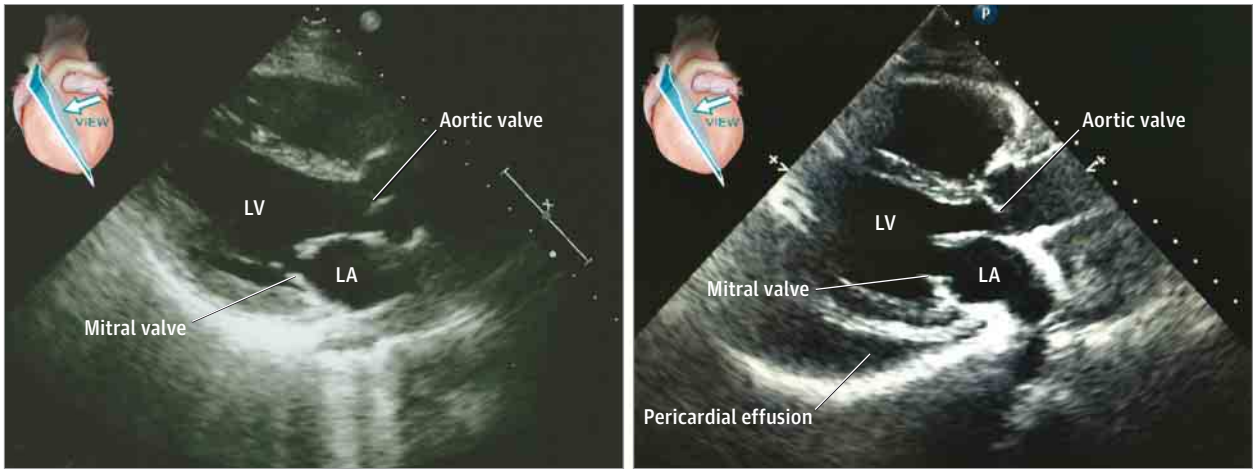
Assessment and Diagnosis

The only available international guidelines on pericardial diseases were published in 2004 by the European Society of Cardiology (ESC)[27] for the first time and updated in 2015.[28] Although the first edition did not provide criteria for diagnosing pericarditis, the 2015 ESC updated guidelines[28] acknowledged and adopted diagnostic criteria published in more recent clinical trials[2,14] (level of evidence C). The diagnosis of acute and recurrent pericarditis is based on specific clinical criteria (**Box 2**). Some patients may present with recurrent chest pain without objective evidence of disease. This phenomenon is more common among people with chronic pericarditis and

Figure 2. Transthoracic 2-Dimensional Echocardiogram Images From 2 Patients With Acute Pericarditis

A Parasternal long-axis view showing acute pericarditis without pericardial effusion

B Parasternal long-axis view showing acute pericarditis with pericardial effusion



A, Parasternal long axis view showing "dry" (without pericardial effusion) acute pericarditis characterized by increased brightness of the pericardial layers, a nonspecific echocardiographic sign associated with fibrinous pericarditis. B, Parasternal long axis view showing a moderate (10-20 mm of telediastolic echo-free space) pericardial effusion. Semiquantitative assessment of pericardial effusion is performed measuring the largest telediastolic echo-free space in different echocardiographic views. A mild effusion is defined as <10 mm; moderate, between 10 and 20 mm; and large, >20 mm.[5,19] A large effusion is associated with an increased risk of complications and with specific etiologies (nonidiopathic pericarditis; nonviral pericarditis). About 60% of patients with acute pericarditis will have a pericardial effusion, generally mild.[5,19] The absence of a pericardial effusion does not exclude pericarditis. LA indicates left atrium; LV, left ventricle.

in patients treated with corticosteroids. However, limited data are available. In a prospective cohort study of 275 patients with acute pericarditis, recurrent pain that did not meet objective criteria for pericarditis recurrence was reported in about 10% of patients. Female sex (odds ratio [OR], 4.3; 95% CI, 1.8-10.6), previous corticosteroid use (OR, 5.2; 95% CI, 2.2-12.3), and recurrent pericarditis (OR, 3.7; 95% CI, 1.3-10.2) were associated with a higher incidence of recurrent chest pain without objective evidence of pericarditis.[29] After a mean follow-up of 40 months, these patients had a higher recurrence rate that met diagnostic criteria (33.3% vs 14.1%; $P = .02$).[29]

In patients without a symptom-free interval of at least 4 to 6 weeks (generally the duration of proposed medical therapy and drug tapering for pericarditis), the term *incessant pericarditis* has been proposed by experts rather than *recurrent pericarditis* because it is characterized by continuous or intermittent symptoms without remission.[2,28]

In addition to the diagnostic criteria specified above, a consensus statement of the American Society of Echocardiography on integrated cardiovascular imaging of pericardial diseases,[20] elevated or ultrasensitive C-reactive protein, and late gadolinium enhancement of pericardium on cardiac magnetic resonance imaging were proposed as additional confirmatory criteria of pericarditis (level of evidence C).

Limited data are available regarding the diagnostic utility of pericardial fluid analysis. Pericardiocentesis is usually not indicated in all patients presenting with acute pericarditis. Specific indications for pericardiocentesis include cardiac tamponade, large symptomatic pericardial effusion not responsive to medical therapy, and suspected bacterial or neoplastic etiology. Biochemical and cell-count composition are generally not helpful for diagnosing most pericarditis.[30] Data on sensitivity and specificity of other pericardial fluid diagnostic tools are limited to specific laboratory tests for diagnosing tuberculous or neoplastic pericarditis (eTable 2 in the Supplement).[31-36] Contemporary diagnosis and management of pericarditis may best be accomplished with an integrated, multimodal approach. Two recent consensus documents, one from the American Society of Echocardiography[20] and one from the European Association of Cardiovascular Imaging,[21] provide imaging and diagnostic considerations based on expert opinion (level of evidence C). Multimodal imaging, including first-level imaging techniques such as echocardiography and chest x-ray (Figure 2 and **Figure 3**) and second-level imaging techniques such as computed tomography and cardiac magnetic resonance, allows detection and confirmation of pericardial inflammation (**Figure 4**), evaluation of pericardial thickness and assessment of the presence of constrictive and/or effusive-constrictive physiology, and establishment of the diagnosis of pericarditis in doubtful cases. These techniques also allow identification of potentially reversible constriction due to pericardial inflammation.[20-22] Additional diagnostic testing is warranted depending on specific clinical suspicion (eTable 3 in the Supplement).

Treatment of Idiopathic, Viral, and Immune-Mediated Pericarditis

Aspirin or NSAIDs

NSAIDs are the mainstay of medical therapy for acute and recurrent pericarditis (**Table 2**) that is idiopathic or viral in etiology (ie, in the absence of a specific cause that may require targeted therapy such as tuberculous and other bacterial etiologies and neoplastic pericardial disease). Only a single clinical trial evaluated the efficacy of NSAIDs, and it was conducted in patients with postpericardiotomy syndrome, a specific form of pericarditis (level of evidence B). In this double-blind RCT of a 10-day course of ibuprofen or indomethacin vs placebo in 149 patients with postpericardiotomy syndrome after cardiac surgery,[11] drug efficacy was defined as resolution of at least 2 of the following: fever, chest pain, and friction rub within

Box 2. Diagnostic Criteria

Diagnostic Criteria for Acute Pericarditis

At least 2 of the following clinical criteria are required:

- Chest pain (typically sharp and pleuritic, improved by sitting up and leaning forward)
- Pericardial friction rub
- Suggestive changes on electrocardiography (widespread ST-segment elevation or PR depression) (Figure 1)
- New or worsening pericardial effusion (Figure 2).

Diagnostic Criteria for Recurrent Pericarditis

The following 3 criteria are all present:

- Documented first attack of acute pericarditis according to diagnostic criteria
- Symptom-free interval of 4 to 6 weeks or longer
- Evidence of subsequent recurrence of pericarditis by recurrent pain combined with 1 or more of the following signs: pericardial friction rub, changes on electrocardiography, echocardiographic evidence of new or worsening pericardial effusion, and elevation in white blood cell count, erythrocyte sedimentation rate, or C-reactive protein level (any value above the upper limit of normal for the laboratory)

Additional Supportive Criteria for Pericarditis (Either Acute or Recurrent)

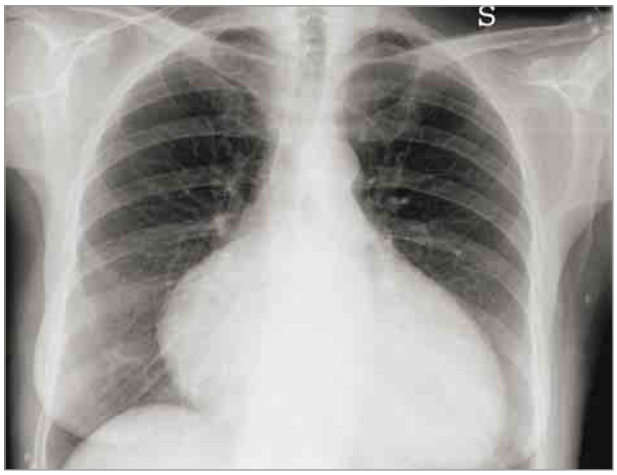
- Elevation of markers of inflammation (eg, C-reactive protein)
- Evidence of pericardial inflammation by an imaging technique (eg, contrast-enhanced pericardium on computed tomography or pericardial edema and pericardial late gadolinium enhancement on cardiac magnetic resonance imaging)[20,28]

48 hours. Ibuprofen and indomethacin were 90.2% and 88.7% effective, respectively. Both were significantly more effective than placebo (62.5%; *P* = .003).

Corticosteroids

Corticosteroid therapy was previously the initial choice for treating pericarditis with pericardial effusions or recurrences not responding to aspirin or NSAIDs. However, more recently, this therapy has been shown to be associated with more adverse effects, possibly a more prolonged disease course, and a higher recurrence risk in nonrandomized studies (level of evidence B). In the largest such study,[22] 100 consecutive patients with recurrent pericarditis (either idiopathic or associated with a systemic inflammatory disease or postcardiac injury syndrome) were evaluated according to a protocol comparing high-dosage prednisone (1.0 mg/kg per day) vs low- to moderate-dosage prednisone (0.2-0.5 mg/kg per day). Each initial dose was maintained for 4 weeks and then slowly tapered. After adjusting for confounders (age, female sex, nonidiopathic origin), only high dosages of prednisone were associated with severe adverse effects, recurrences, and hospitalizations (hazard ratio [HR], 3.61; 95% CI, 1.96-6.63). Hospitalizations were lower in patients treated with low- vs high-dosage prednisone (8.2% vs 31.4%, respectively; *P* = .005). Use of low to moderate dosages of corticosteroids was associated with a lower recurrence rate during follow-up compared with high dosages (eg, prednisone, 1.0 mg/kg/d) (32.6% vs 64.7%; *P* = .002).

Figure 3. Posterior-Anterior Chest Radiograph of a Patient With Acute Pericarditis



Water bottle–shaped cardiac silhouette characteristic of a large pericardial effusion in a patient with acute pericarditis. Chest radiograph findings in patients with acute pericarditis are typically normal unless there is concomitant pleuropulmonary disease or a very large pericardial effusion (>300 mL).

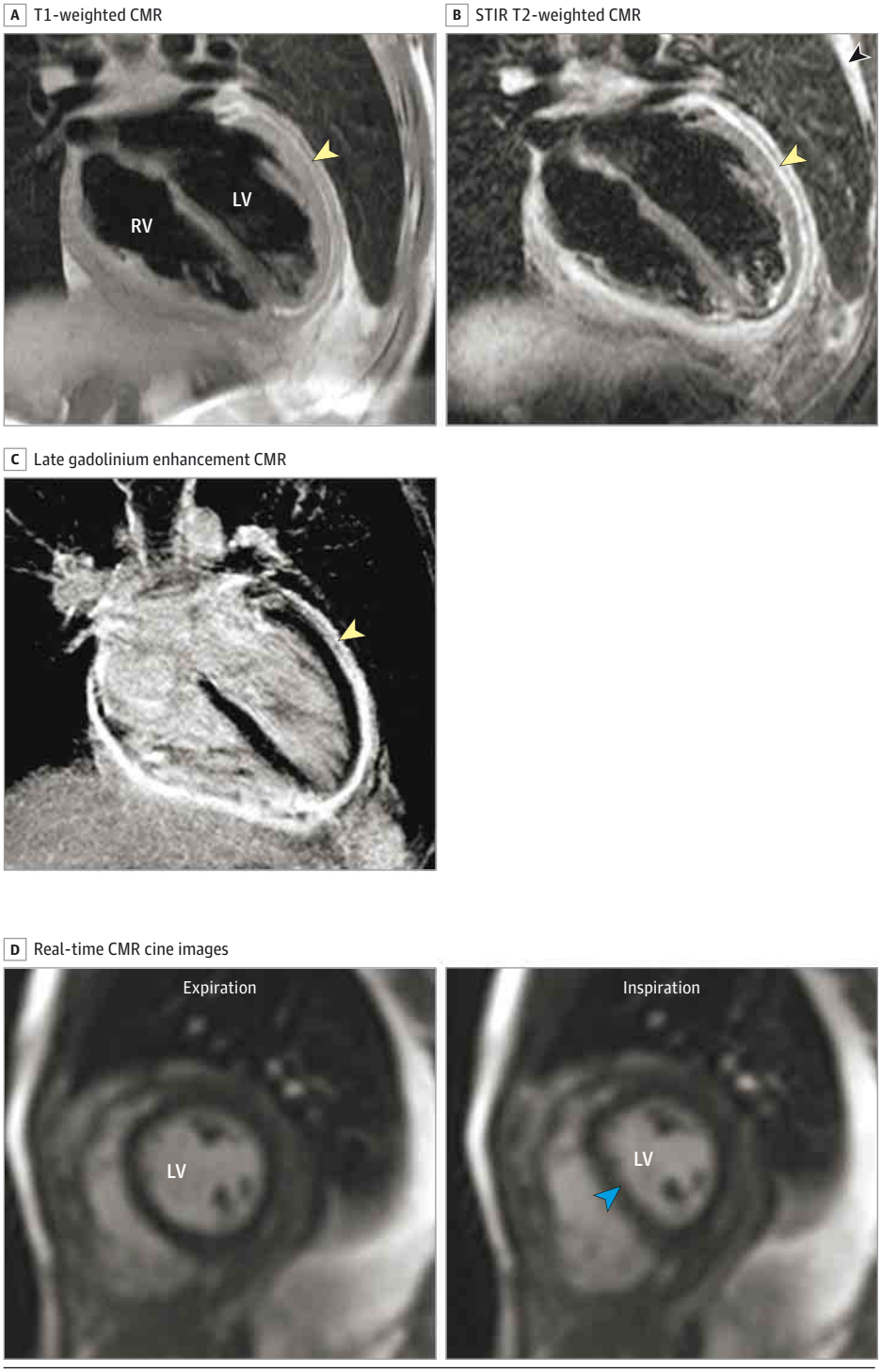
Colchicine

Considerable evidence supports using colchicine as an adjunct to NSAIDs to improve remission rates at 1 week and reduce recurrence rates in both acute[1,2] and recurrent pericarditis[14,16,18] compared with NSAIDs alone (level of evidence A).

The main known anti-inflammatory effect of colchicine is blockade of tubulin polymerization with impaired microtubule assembly, thus inhibiting the pro-inflammatory functions of white blood cells, especially granulocytes, where colchicine concentrates. In a meta-analysis[37] including 7 studies of medical therapy for pericarditis (idiopathic, viral, or due to inflammatory systemic disease or postcardiac injury syndrome) that included 451 patients, treatment comparisons were colchicine plus NSAIDs vs NSAIDs only (3 RCTs; 265 patients), corticosteroids vs NSAIDs (2 observational studies; 31 patients), low-dosage vs high-dosage corticosteroids (1 observational study; 100 patients), and statins vs standard therapy (1 RCT; 55 patients). Colchicine was associated with a reduced risk of treatment failure (OR, 0.23; 95% CI, 0.11-0.49) and recurrent pericarditis (OR, 0.39; 95% CI, 0.20-0.77). The most common adverse event associated with colchicine is gastrointestinal intolerance, especially diarrhea, reported in 7% to 10% of patients receiving colchicine therapy. Low-dosage corticosteroids (eg, prednisone, 0.2-0.5 mg/kg per day) were associated with lower rates of recurrence or treatment failure (OR, 0.29; 95% CI, 0.13-0.66), hospitalizations (OR, 0.19; 95% CI, 0.06-0.63), and adverse effects (OR, 0.07; 95% CI, 0.01-0.54) compared with high-dosage corticosteroids (eg, prednisone 1.0 mg/kg per day). Data on statins were inconclusive and derived from a single-center study without additional supporting evidence.

Additional meta-analyses[38-40] including the last RCT[13] reported that colchicine use was associated with a reduced risk of postpericardiotomy syndrome (OR, 0.48; 95% CI, 0.33-0.68) and recurrent pericarditis in patients with acute pericarditis (OR, 0.31; 95% CI, 0.19-0.52) or recurrent pericarditis (OR, 0.31; 95% CI, 0.20-0.46) (level of evidence A). The use of colchicine was associated with an increased

Figure 4. Cardiac Magnetic Resonance Images From a Patient With Acute Pericarditis



Findings characteristic of acute pericarditis that may be observed with cardiac magnetic resonance (CMR) imaging include pericardial thickening and evidence of pericardial edema. A, T1-weighted 4-chamber view showing thickened pericardium (yellow arrowhead). B, STIR T2-weighted 4-chamber view showing a pericardial hyperintense signal (yellow arrowhead) that indicates increased pericardial edema and left pleural effusion (black arrowhead). C, Late gadolinium enhancement 4-chamber view showing late enhancement of the pericardium (yellow arrowhead). Late gadolinium enhancement may persist beyond the acute phase of pericarditis indicating organizing pericarditis (chronic inflammatory pericarditis and fibrosis). D, Real-time free-breathing cine images, midventricular short-axis views, in expiration (left) and inspiration (right) showing septal flattening during inspiration (blue arrowhead), indicating accentuated interventricular independence. Images courtesy of Patrizia Pedrotti, MD, Giuseppina Quattrocchi, MD, and Alberto Roghi, MD, Ospedale Niguarda, Milan, Italy.

risk of adverse events (mainly diarrhea; OR, 1.45; 95% CI, 1.04.2-03) and drug discontinuation (OR, 1.40; 95% CI, 1.00-1.94).

In more recent trials, efficacy was achieved without an initial loading dose and by prescribing weight-adjusted dosages (eg, 0.5 mg twice daily in patients >70 kg and 0.5 mg once daily in patients ≤70 kg).[2,14] On this basis, weight-adjusted dosing of colchicine without a loading dose is recommended in patients with acute and recurrent pericarditis in addition to aspirin or an NSAID (level of evidence A).

New Therapeutic Options for Recurrent Pericarditis After Failure of Colchicine Treatment

Optimal management of patients with multiple recurrences and patients either who do not tolerate colchicine or in whom colchicine therapy has failed is unclear. There is limited evidence to support alternative therapies including oral azathioprine,[41] intravenous human immunoglobulins,[42,43] and anakinra (an interleukin-1 receptor antagonist).[44,45] In the management of recurrent pericarditis, aza-

thioprine acts as immunosuppressive therapy while intravenous immunoglobulins and anakinra act as immunomodulatory agents.

For patients with refractory recurrent pericarditis that is not responsive to any medical therapy, the last therapeutic option is pericardiectomy. However, this therapy is only supported by a retrospective series from the Mayo Clinic, which demonstrated that patients with recurrent pericarditis who received surgery experienced fewer relapses than patients with recurrent pericarditis who received medical therapy (level of evidence C).[46] In contrast, a small retrospective study found that few patients (2 of 9 patients) responded to pericardiectomy.[47] Both of these studies are limited by their retrospective design.

Prognosis

An Italian prospective cohort study evaluated the risk of complications during follow-up of 453 patients aged 17 to 90 years.[19] A specific cause of pericarditis was found in 76 patients (16.8%). The etiology of pericarditis was autoimmune in 33 patients (7.3%), neoplastic in 23 (5.1%), tuberculous in 17 (3.8%), and purulent in 3 (0.7%). In multivariable analysis, female sex (HR, 1.67; 95% CI, 1.03-2.70; $P = .04$) and patients with fever higher than 38°C or 100.4°F (HR, 3.56; 95% CI, 1.82-6.95; $P < .001$), subacute course (HR, 3.97; 95% CI, 1.66-9.50; $P = .002$), large effusion or tamponade (HR, 2.15; 95% CI, 1.09-4.23; $P = .03$), and failure of NSAID therapy (including aspirin) (HR, 2.50, 95% CI, 1.28 to 4.91; $P = .008$) were associated with an increased incidence of an identifiable cause of the pericarditis. After a mean follow-up of 31 months, the following complications were detected in 95 patients (21.0%): recurrences in 83 (18.3%), tamponade in 14 (3.1%), and constriction in 7 (1.5%). In multivariate analysis, female sex (HR, 1.65; 95% CI, 1.08-2.52; $P = .02$), large effusion or tamponade (HR, 2.51; 95% CI, 1.37-4.61; $P = .003$), and failure of NSAID therapy (HR, 5.50; 95% CI, 3.56-8.51; $P < .001$) were associated with an increased risk of complications, which were reported more commonly in patients with a nonidiopathic etiology of pericarditis. On this basis, specific clinical features (fever >38°C or >100.4°F, subacute course, large effusion or tamponade, and NSAID/aspirin therapy failure) were proposed as indicators of an identifiable cause of pericarditis and poor prognosis and, in addition, a rationale for hospital admission (level of evidence B) (eFigure 2 in the Supplement).

A single prospective cohort study evaluated complication rates in patients with pericarditis of varying etiologies with a special focus on the risk of developing constrictive pericarditis.[7] Five hundred consecutive cases with a first episode of acute pericarditis (age 51 ± 16 years; 270 men) were prospectively studied. Etiologies were viral/idiopathic in 416 cases (83.2%), connective tissue disease/pericardial injury syndromes in 36 (7.2%), neoplastic pericarditis in 25 (5.0%), tuberculosis in 20 (4.0%), and purulent in 3 (0.6%). During a median follow-up of 72 months (range, 24-120 months), constrictive pericarditis developed in 9 of 500 patients (1.8%): 2 of 416 patients with idiopathic/viral pericarditis (0.48%) vs 7 of 84 patients with other etiologies (8.3%). The incidence of constrictive pericarditis was 0.76 cases per 1000 person-years for idiopathic/viral pericarditis, 4.40 cases per 1000 person-years for connective tissue disease/pericardial injury syndrome, 6.33 cases per 1000 person-years for neoplastic pericarditis, 31.65 cases for 1000 person-years for tuberculous pericarditis, and 52.74 cases per 1000 person-years for purulent pericarditis. This study indicates that development of constrictive pericarditis is related to etiology (level of evidence B).

Table 2. Therapies for Acute and Recurrent Pericarditis by Indication and Rating Based on Quality of Available Evidence[a]

Therapy	Level of Evidence[b]	Mechanism of Action
Aspirin/nonsteroidal anti-inflammatory drugs		
Aspirin, 750-1000 mg 3 times daily; ibuprofen, 600 mg 3 times daily; indomethacin, 25-50 mg 3 times daily; all usually for 1-2 wk in acute pericarditis and 2-4 in recurrent pericarditis, then tapered[11,30,bc]	B	Inhibition of the activity of both cyclooxygenase-1 and cyclooxygenase-2 and thereby the synthesis of prostaglandins
Colchicine, 0.5 mg twice daily or once daily for 3 mo (acute) or 6 mo (recurrent); once daily if weight ≤70 kg[1,2,14,16,18,30-33]	A	Blocking of tubulin polymerization, reduction of microtubule and granulocyte function
Corticosteroids, 0.2-0.5 mg of prednisone or equivalent, usually for 2-4 wk, then tapered[1,18,19,30,c]	B	Suppression of most components of the inflammatory process
Azathioprine, 1.5-2.5 mg/kg per d for several mo[34]	C	Blocking of purine and DNA synthesis and inhibition of lymphocyte proliferation
Intravenous immunoglobulins (400-500 mg/kg per d for 5 d)[35]	C	Modulation of adaptive and innate immunity and increased clearance of infectious agents
Subcutaneous anakinra (1-2 mg/kg per d up to 100 mg for several mo)[37]	C	Competition with interleukin 1 and reduction of interleukin-1 activity

[a] Including largest studies on adult populations. These therapies are indicated for idiopathic and nonbacterial etiologies.

[b] Available levels of evidence for each diagnostic intervention were reviewed and classified according to American Heart Association/American College of Cardiology guidelines as follows: level A if data are available from multiple populations based on clinical trials or registries delineating usefulness/efficacy in various subpopulations; level B if limited populations have been evaluated and/or data are derived from a single randomized clinical trial or nonrandomized studies; and level C if very limited populations have been evaluated or only consensus opinion of experts, case studies, and unverified standards of care are available.

[c] Until symptom resolution and normalization of markers of inflammation (eg, C-reactive protein).

Pericarditis and myocarditis may coexist in 20% to 30% of patients presenting with a clinical suspicion of pericarditis due to overlapping etiologies (all causes of pericarditis are also potential causes of myocarditis).[48-51] The presence of concomitant myocarditis is often indicated by elevation of serum troponins. Patients with pericarditis concomitant with myocarditis (usually referred as myopericarditis) have potential for a higher rate of complications including left ventricular dysfunction and heart failure. In a recently published systematic review of myopericarditis,[49] 8 major clinical series were included with a total of 389 patients (mean age, 31.7 years; male-female ratio, 4.0). After a mean follow-up of 31 months, residual left ventricular dysfunction was reported in 3.5% with no cases of heart failure. Recurrences occurred in 13.0% of cases, mainly as recurrent pericarditis (>90%), with cardiac tamponade and constrictive pericarditis in less than 1% of cases.

In the largest study,[23] no deaths were recorded, there was no progression to heart failure, and troponin elevation was not associated with an increase in complications (level of evidence B). In this study, a clinical diagnosis of myopericarditis was made in patients with a definite diagnosis of acute pericarditis and elevation of cardiac markers of injury (troponin I or T, creatine kinase–MB fraction)

without new onset of focal or diffuse depressed left ventricular function by echocardiography or cardiac magnetic resonance imaging.

A systematic review of all published cases of idiopathic recurrent pericarditis without myocarditis[52] included 8 major clinical series with a total of 230 patients (mean age, 46 years; male-female ratio, 0.9). After a mean follow-up of 61 months, cardiac tamponade occurred in 3.5% of cases, and no cases of constrictive pericarditis or left ventricular dysfunction occurred. The overall prognosis was excellent in idiopathic recurrent pericarditis with low morbidity rates, leading to the conclusion that constrictive pericarditis virtually never occurs after idiopathic pericarditis, even though idiopathic pericarditis can recur (level of evidence C), and the risk is actually lower than in idiopathic acute pericarditis without recurrence, in which the reported risk is approximately 1%.

Clinical Practice Guidelines

International practice guidelines for pericarditis were recently updated by the ESC.[28] The guidelines incorporate diagnostic criteria and a new set of recommendations that are mainly based on expert opinion. Similarly, recent consensus updates focus on multimodal imaging of pericardial disease and are mainly based on expert opinion (eTable 4 in the Supplement).[20,21]

The findings of the review are consistent with current clinical practice guidelines, that, however, provide especially a European perspective. On this basis, there is a need for additional research to address potential issues related to different ethnicities and developing countries.

Discussion

The diagnosis of pericarditis should be based on clinical criteria (Box 2). Basic diagnostic assessment (clinical evaluation, electrocardiogram, routine blood chemistry, markers of inflammation and myocardial lesion (eg, troponins), chest x-ray, and echocardiogram) may allow the clinician to select patients at high risk of nonidiopathic/nonviral etiologies and complications warranting hospital admission, as well as appropriate diagnostic evaluation.

Based mainly on expert consensus, a single RCT in the setting of the postpericardiotomy syndrome,[11] and a meta-analysis (level of evidence B),[37] the mainstay of anti-inflammatory therapy for nonbacterial causes of pericarditis is an NSAID, most commonly ibuprofen or aspirin.[28] Colchicine should be combined with standard anti-inflammatory therapy to hasten the response to medical therapy and prevent recurrences in patients with nonbacterial causes. This statement is supported by several RCTs,[1,2,14,16,18] meta-analyses,[37-40] and the 2015 ESC guidelines[28] (level of evidence A). In the absence of a specific indication (eg, systemic inflammatory diseases requiring corticosteroids, pregnancy), corticosteroids are associated with an increased risk of recurrences,[23,37] especially when prescribed in high dosages (eg, prednisone, 1 mg/kg per day)[23] (level of evidence A). Thus, corticosteroid therapy should be restricted to patients who do not tolerate NSAIDs or who have contraindications to their use, and only after failure of first-line therapy combined with colchicine. Newer therapies (eg, intravenous immunoglobulins and anakinra) may be considered for patients who do not respond to colchicine, but additional evidence is needed to confirm their efficacy. Pericardiectomy is a final option in experienced surgical centers after failure of medical therapies.

The optimal duration of anti-inflammatory therapy is unclear. An individualized approach is advisable. Clinicians should consider both symptom resolution and normalization of inflammatory biomarkers (eg, C-reactive protein) to guide the duration of anti-inflammatory therapy (usually 1-2 weeks).[53] Tapering (usually with an overall 4- to 6-week course of therapy) may be considered to reduce the risk of recurrences (level of evidence B). This approach has been recently endorsed by the 2015 ESC guidelines.[28]

The role of nonpharmacological measures is not well established, but they are part of the recommended therapy. Although exercise restriction in the setting of pericarditis has been recommended,[5,6] this recommendation is based only on expert opinion, and there are no observational studies or clinical trials for or against this recommendation (level of evidence C). Currently, exercise restriction is recommended until remission for nonathletes and until remission but with a minimal arbitrary period of 3 months for athletes, according to expert consensus.[28]

There is no clinical trial evidence to guide management of myopericarditis. Myopericarditis is associated with low rates of morbidity, mortality, evolution to heart failure, and worsening ventricular function.[49]

Future research should focus on specific subpopulations: children, women, elderly people, and individuals of varying ethnicities.[54-56] Currently, most data are from white patients, with only limited data in specific populations, mainly among those with tuberculous pericarditis from sub-Saharan Africa.[8] Moreover, further prospective studies are needed to elucidate the etiology and epidemiology of pericarditis as well as optimal therapies, especially for patients with recurrent pericarditis and those not responsive to NSAIDs and colchicine.

ARTICLE INFORMATION

Author Contributions: Dr Imazio had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: Imazio, LeWinter.
Drafting of the manuscript: Imazio, LeWinter.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Imazio.
Administrative, technical, or material support: Imazio.
Study supervision: All authors.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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