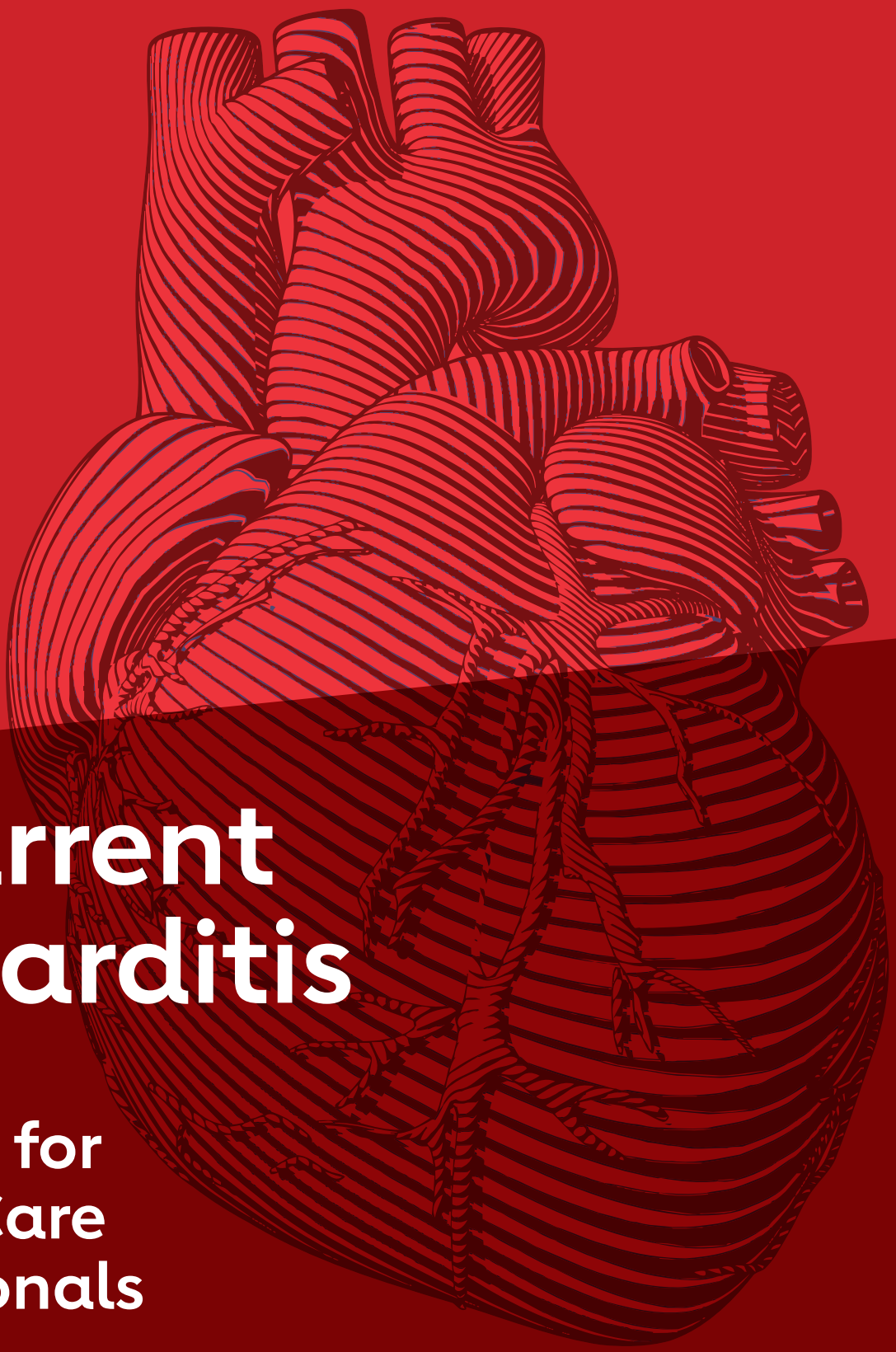
American Heart Association.



Recurrent Pericarditis

A Toolkit for Health Care Professionals

Kiniksa Pharmaceuticals is a proud supporter of the American Heart Association's Addressing Recurrent Pericarditis educational content.

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Disclaimer: This toolkit incorporates therapeutic information from the 2025 European Society of Cardiology Guidelines for the management of myocarditis and pericarditis, which currently constitute the most comprehensive, evidence-based recommendations available in the absence of an American Heart Association pericarditis guideline. However, drug approvals and market availability differ across jurisdictions. While certain interleukin-1 (IL-1) inhibitors — such as anakinra and canakinumab — are authorized in both the United States and the European Union, they are not approved specifically for recurrent pericarditis. Other agents, like rilonacept (approved in the U.S.) or goflikicept (approved in Russia), may be available only in select regions. Clinicians should adhere to best practices based on current evidence and the therapeutics available in their region. The inclusion or mention of any pharmaceutical product does not constitute Heart Association endorsement.

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Introduction

Pericarditis is an important clinical problem and accounts for up to 5% of emergency admissions with acute chest pain. It remains the most common cause of pericardial disease worldwide.[1-3] Nevertheless, dedicated pericardial clinics and acute pericardial services are few, and most patients present to and are managed by primary care physicians, emergency physicians or general cardiologists.

Most patients respond to first-line treatment and experience a benign disease trajectory with eventual resolution of symptoms and no long-term sequelae. However, approximately 30% of patients can go on to develop recurrent pericarditis, which can have a dramatic deleterious effect on quality of life as well as result in increased utilization of health care resources.[4,5]

Although many challenges remain, the last decade has witnessed significant advances in our understanding of the pathophysiology of inflammatory pericardial disease as well as several important therapeutic advances. With timely and effective evidence-based initial care, the incidence of recurrent pericarditis can be halved,[2] and for those who do go on to develop this complication, newer treatment options are now available.[6]

The aim of this American Heart Association toolkit is to equip all clinicians who may encounter patients with acute pericarditis with the knowledge, skills and practical guidance to manage acute and recurrent pericarditis confidently and effectively. The Recurrent Pericarditis Toolkit has been assembled by an international and multidisciplinary team of experts. It strongly emphasizes practical guidance for issues clinicians are likely to encounter in day-to-day, clinical practice, buttressed where necessary with the theoretical basis for the guidance.

The toolkit is supported by a series of four American Heart Association vodcasts and webinars, which in turn build on an extensive library of resources available on the **Lifelong Learning website (https://professional.heart.org/en/education/recurrent-pericarditis-for-professionals).**

Pericardial Anatomy, Structure and Function

The pericardium is the outer lining of the heart consisting of an inner double-layered sac called the serous pericardium. The inner layer of the sac is the visceral layer, or epicardium, that lines the heart and proximal great vessels. The visceral layer is reflected to form the parietal pericardium, which lines the fibrous pericardium.[7]

The pericardial cavity exists between the two layers, which contain approximately 15-50 ml of plasma infiltrate.[7] Anchoring the heart in the thorax, the pericardium acts as a mechanical protective layer for the heart against trauma and as an immunologic barrier.[1] The pericardial fluid serves as a lubricant to reduce friction between the heart and its surrounding structures and eases movement during the twisting, contracting and relaxation actions.

Hemodynamic effects of the pericardium occur in response to changes in intrathoracic pressure, which cause changes in pericardial and intracardiac pressure with slight increases in left ventricular (LV) stroke volume and arterial blood pressure. During inspiration, the negative intrathoracic pressure increases venous return to the right heart and slightly reduces LV filling unrelated to the normal pericardium.

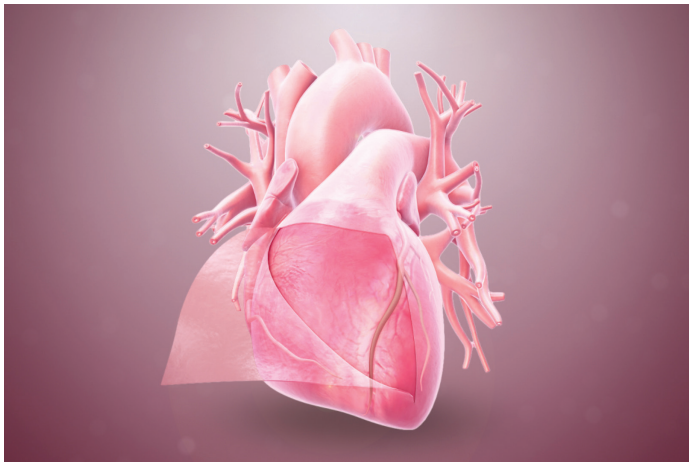

Illustration of the heart showing the pericardial layers.

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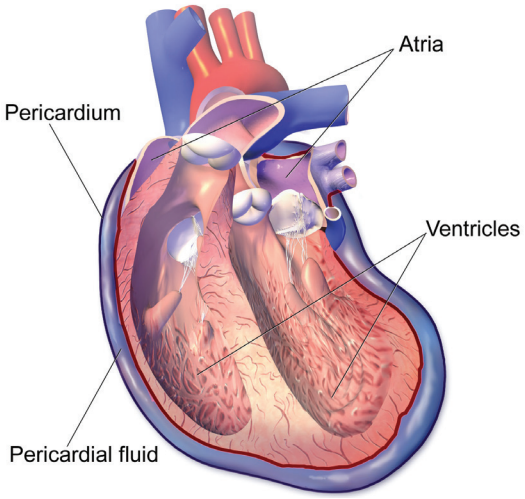

Inflammation of the pericardium.

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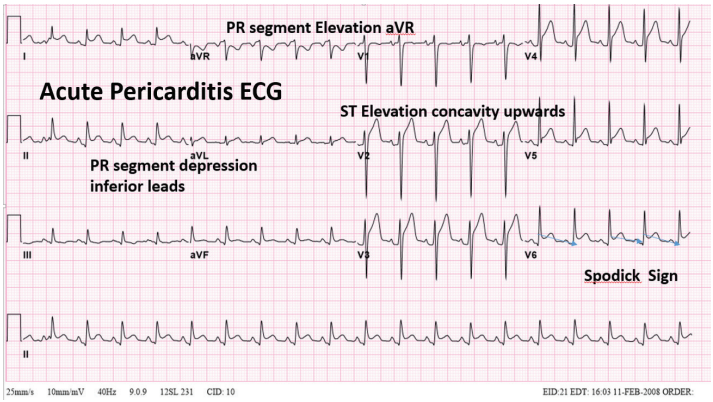

The ECG in acute pericarditis.

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Acute pericarditis is an inflammatory pericardial syndrome with or without pericardial effusion, typically presenting within four weeks of symptom onset. It occurs more often in males aged 20–50 years,[8] and most cases are idiopathic and presumed to be post-viral.[9]

In developing countries with a high prevalence, tuberculosis (TB) with or without HIV co-infection is a common cause of pericarditis. In developed countries with a low prevalence of TB, conditions causing pericarditis are systemic inflammation, cancers such as lung, breast, lymphomas and leukemia, chest irradiation, post-cardiac surgery injury syndromes, including pericarditis post-myocardial infarction, percutaneous coronary intervention and electrophysiology procedures or post-pericardiectomy.[9,10]

The diagnosis is made with a clinical presentation including chest pain or infarct-like symptoms, arrhythmias, heart failure or aborted sudden cardiac death.

Diagnostic criteria have evolved with the publication of the 2025 European Society of Cardiology (ESC) Guidelines, placing more emphasis on the clinical presence of classic chest pain or equivalent.

1. Clinical presentation: pleuritic/infarct-like chest pain (present in 85-90% of cases) or equivalent
2. Plus ≥1 additional finding (0 = unlikely/rejected, 1 = possible, and 2+ = definite diagnosis):
   a. Pericardial friction rub
   b. Electrocardiogram changes consisting of diffuse ST-segment elevation and/or PR-segment depression
   c. Inflammatory biomarkers elevation (such as C-reactive protein [CRP] or sedimentation rate)
   d. Cardiac imaging (especially echocardiography evidence) of new or worsening pericardial effusion
   e. Cardiac imaging evidence of pericardial inflammation

Diagnostic workup includes a review of past medical history, physical examination with a focus on heart auscultation, chest X-ray, electrocardiogram, echocardiography and laboratory tests for markers of inflammation [C-Reactive Protein (CRP)], troponin and thyroid levels.[11]

Further investigation is not recommended since most often the cause is viral or idiopathic. For patients experiencing high fever [>38° C (>100.4° F)], subacute course, development of a large pericardial effusion, cardiac tamponade or no response to nonsteroidal anti-inflammatory drugs >7 days warrant more extensive diagnostic testing.[12]

Recurrent pericarditis may occur in approximately 20%-30% of patients as a complication of acute pericarditis after a symptom-free interval. Diagnostic testing is similar to that done in the acute phase. It occurs more commonly in those who were not treated with colchicine.[13]

The 2025 ESC Guidelines recommend testing for elevated markers of inflammation, such as CRP, ESR and neutrophilic leukocytosis, to provide additional diagnostic supportive criteria. CT is recommended to evaluate pericardial thickness, calcifications, masses and loculated pericardial effusions as well as concomitant pleuropulmonary diseases and chest abnormalities. CMR is recommended in patients with suspected pericarditis when a diagnosis cannot be made using clinical criteria to assess evidence of pericardial thickening, edema or LGE and to assess the persistence of disease during follow-up in selected cases.[14]

Incessant pericarditis is defined as patients with persistent symptoms lasting longer than four to six weeks *(but less than three months)* who have no clear period of remission after the acute episode. The probability of developing incessant pericarditis as reported by Cremar et al. (2016) is approximately 15%–20%.[12]

Chronic pericarditis refers to patients who have symptoms lasting longer than three months.[12]

Constrictive pericarditis is an uncommon complication of viral pericarditis, occurring in less than 1% of cases, but can occur in any form of pericarditis, except rarely with recurrent pericarditis.[1,8,13] Development of fibrous thickening or calcification of the pericardium results in pericardial noncompliance presenting as a clinical form of heart failure.[7,12,13,15]

The hemodynamic alterations occurring in constrictive pericarditis are the dissociation of intrathoracic-intracardiac pressures and enhanced ventricular interaction.[13,15] On inspiration, the noncompliant pericardial sac impedes the transmission of pressure in the pulmonary veins to the left ventricle (LV), causing an inspiratory reduction in venous return to the LV and permitting the ventricular septum to move toward the LV. During inspiration, the right ventricle (RV) stroke volume increases, and the LV stroke volume decreases, resulting in the pulsus paradoxus, a decrease in blood pressure greater than 10 mm Hg with inspiration.[7,13,15]

Symptom presentation includes fatigue, peripheral edema, dyspnea and abdominal distention. Physical examination findings may include jugular venous distention, increased central venous pressure and hepatomegaly. The central venous pressure may be so high that the examiner has the patient stand up to appreciate venous pulsations.[12,16]

Diagnostic testing includes chest X-ray, echocardiography, CT, CMR and cardiac catheterization in determining a differential diagnosis. Laboratory findings include slight elevations in creatinine and liver enzymes (alkaline phosphatase).[7,12,13,15]

There are three subtypes of constrictive pericarditis as described by Adler et al. (2015):[1]

Transient constrictive pericarditis

This is a temporary form of constriction due to the inflammation occurring with pericarditis, usually involving a mild effusion. It resolves once the inflammation subsides after a course of anti-inflammatory therapy.

Effusive constrictive pericarditis

Although pericardial fluid is typically not present in patients with constrictive pericarditis, for some a pericardial effusion further restricts cardiac filling and can cause cardiac tamponade. It is an uncommon occurrence in developed countries, usually with idiopathic pericarditis, but can be associated with radiation, neoplasm, chemotherapy, infection (especially TB and purulent forms) and post-surgical pericardial disease. Pericardiocentesis and monitoring of intracardiac pressures, such as right heart pressure and systemic arterial blood pressure, are recommended. CMR can be useful in evaluating pericardial thickness, cardiac morphology and function.

Chronic constrictive pericarditis

Characterized as a persistent constriction lasting longer than three to six months, it may exhibit heart failure NYHA class III or IV symptoms.

Structured History Taking for Acute Pericarditis

The goal of history taking is to:

- Gather data to make a diagnosis
- Exclude important differentials
- Identify features of any relevant systemic disease for which pericarditis may be a manifestation
- Detect comorbidities that may impact therapy
- Anticipate any social or occupational factors that may impinge on ongoing care.

The following is not a comprehensive list, but is intended to highlight questions that are particularly relevant to identifying these features or manifestations of disorders that may accompany pericarditis or complicate its treatment.

Chest pain history

- ☐ A comprehensive chest pain history includes onset, timing, quality, severity, radiation, associated symptoms and exacerbating and relieving factors.
- ☐ Typical chest pain in acute pericarditis is sharp, sudden onset and pleuritic — worse with inspiration or cough, worse laying backward and improved when sitting forward. Referred pain is also common, especially to the shoulder region.
- ☐ In cases of recurrent pericarditis, patients often can sense the pain coming prior to a full-blown episode.
- ☐ A history should also be taken to assess for complications of pericarditis, including clinical tamponade such as syncope, lightheaded/dizziness, nausea and myopericarditis such as those indicative of LV dysfunction — shortness of breath, abdominal swelling and lower extremity edema.

Personal medical and surgical history

- ☐ Any previous episodes of acute pericarditis?
  - ○ What were the circumstances in which these occurred?
  - ○ Were there any complicating features (e.g., incessant course, large effusion, tamponade)?
  - ○ What treatment was given (duration, intensity)?
  - ○ Did the patient adhere to the treatment? If not, why not? Was this due to side effects, medication costs, lack of knowledge?
- ☐ Any previous history of trauma to the chest or interventional cardiac or cardiothoracic surgical procedures?
- ☐ Any past history of asthma and in particular, asthma exacerbation with NSAIDs?
- ☐ Any past history of peptic ulcer disease/GI blood loss, significant gastroesophageal reflux disease, *H. pylori* infection, bleeding diathesis or renal or hepatic impairment?
- ☐ Any history of diabetes mellitus, obesity, osteopenia/osteoporosis/fragility fractures, vitamin D deficiency, coronary disease (which may favor use of aspirin over NSAIDs), hypertension, renal impairment or hepatic dysfunction?
- ☐ Any history of autoimmune rheumatic disease, inflammatory bowel disease, autoinflammatory disease or immunodeficiency (severe, prolonged, recurrent or unusual infections)?
- ☐ Any comorbidities that may necessitate co-prescription of potent cytochrome P450, family 3, subfamily A (CYP3A4) and/or P-glycoprotein inhibitors?
- ☐ Any past history of TB or exposure to this bacterial infection?
- ☐ Any history of abdominal surgery, particularly negative laparotomies?
- ☐ Any history of cancer/radiotherapy?
- ☐ Any psychiatric history (which may be relevant to steroid prescribing and holistic care)?
- ☐ Any history of claustrophobia or implants?

Medications and allergies

- ☐ Any use of anticoagulants or potent antiplatelet therapy or other drugs that may promote GI injury/blood loss, e.g., SSRIs, bisphosphonates?
- ☐ Any potent CYP3A4 or P-glycoprotein inhibitors? (*See "Management of Acute Pericarditis" on page 14.*)
- ☐ Pregnancy (gestation) and breastfeeding?
- ☐ Any known drug allergies or relevant food/excipient allergies?
- ☐ Any history of adverse drug reactions to NSAIDs/colchicine/steroids or exposure to drugs that can trigger systemic lupus erythematosus (SLE) (e.g., hydralazine, procainamide, TNFa-inhibitors)?

Social history

- ☐ Occupational history (impact on job, financial resilience, capacity to abstain from manual work/physical exertion, occupational injury)?
- ☐ Travel history, including travel to countries with high TB prevalence (Africa, S/SE Asia, China and India) or exposure to pathogens, ability to transport/store medication?
- ☐ Smoking history? Encourage smoking cessation, which will also reduce risks of GI ulceration with NSAIDs/steroids.
- ☐ Alcohol history: (relevant to reducing risks of GI upset/ulceration and, where excessive, hepatic dysfunction, which may impact drug metabolism)?
- ☐ Recreational drug misuse or chronic opioid use/chronic pain/addiction?
- ☐ Factors that may impact care: e.g., pets, caring responsibilities, impact of illness on relationships, family, finances?

Family history

Any family history of autoimmune rheumatic disease, inflammatory bowel disease, periodic fever syndromes/autoinflammatory disease. Any family history of TB or TB exposure?

Review of systems

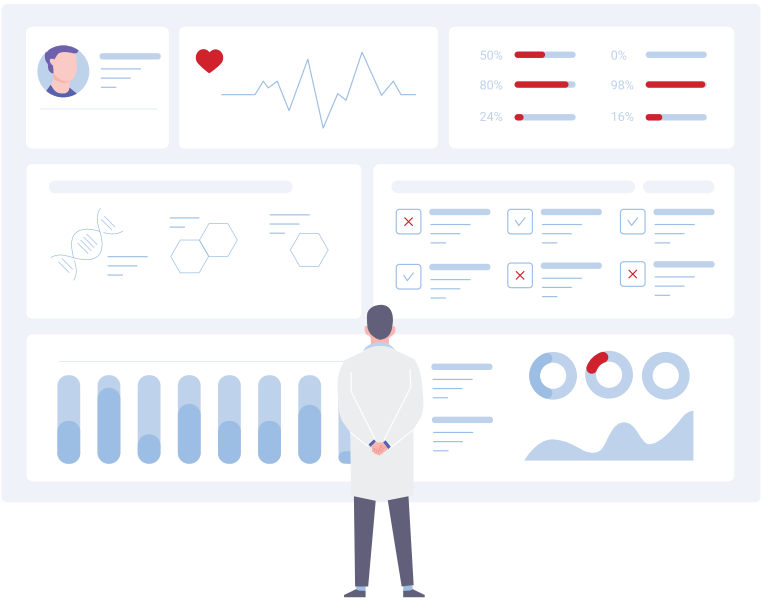
General
Any unexplained malaise/fatigue, anorexia, weight loss, fever/rigors, night sweats, lymphadenopathy, polyuria, polydipsia, insomnia, hypersomnolence.

Respiratory
Pleuritic chest pain, shortness of breath, cough, sputum, hemoptysis, wheeze.

Abdominal
Dysphagia, reflux, peritonitic abdominal pain (especially if recurrent), diarrhea, constipation, change in bowel habit, GI bleeding, hematemesis.

Neurologic
Headache, visual disturbance/diplopia, red eye/discharge, muscle pain, paresthesia/sensory disturbance, neuropsychiatric disturbance.

Musculoskeletal/Rheumatologic/Skin
Arthritis (arthralgia, swelling, erythema, pattern of involvement), enthesitis, alopecia, dry eyes/mouth, photosensitive rash, erysipelas-like rash, conjunctivitis, temperature-related rash, oral/genital ulceration, Raynaud's, digital ulceration.



Differential Diagnosis

The differential diagnosis of those presenting with pericarditis is dependent upon signs and symptoms, prior medical history and acuity. In acute pericarditis, chest pain occurs >95% of the time.[17] Myocardial ischemia (including ST-segment elevation myocardial infarction), aortic dissection, myocarditis (without a pericardial component) and pulmonary embolism should be ruled out or deemed less likely.

Although the age of presentation may influence diagnostic decision-making, up to 30% of myocardial infarctions occur in those <55 years of age,[18] and thus either noninvasive (e.g., computed tomography [CT]) or invasive (angiography) imaging may be required, especially if the ECG changes are not diagnostic of pericarditis.

Given the inflammatory state of pericarditis (with associated leukocytosis and fever), the differential diagnosis of pericarditis often includes infections such as pneumonia. Other common noncardiac causes of acute chest pain consist of gastrointestinal disorders, such as acid reflux, musculoskeletal complaints and fibromyalgia. These conditions can be misdiagnosed as pericarditis, particularly in those with ECGs consistent with early repolarization or left ventricular hypertrophy. In cases of suspected recurrent pericarditis, where the chest pain syndrome may be less severe, normal inflammatory biomarkers and nondiagnostic ancillary imaging should prompt a search for nonpericardial chest pain etiologies.

Patients who present with a pericardial effusion without a high clinical suspicion of pericarditis may at times present a diagnostic dilemma.

In a retrospective analysis of 269 patients with a pericardial effusion requiring pericardiocentesis:

26% were idiopathic

25% were malignant (including 9% as a first diagnosis of a malignancy)

20% were iatrogenic

The rest of the various etiologies included heart failure, uremia, systemic disease and infection.[19]

The underlying causes of pericarditis can be coarsely divided into idiopathic (often assumed to be viral), infectious and noninfectious etiologies.

An antecedent upper respiratory or gastrointestinal tract infection was identified in **up to 40% of patients** presenting with acute pericarditis without a known etiology.[20]

In a series of 1,162 patients with pericarditis:

55% were deemed idiopathic

9% were neoplastic

2.6% were autoimmune.[21]

Viruses implicated in pericarditis include coxsackievirus, adenovirus, influenza, HIV and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In developed countries, bacterial and TB-driven pericarditis is rare; however, in developing countries with a high TB prevalence, this is a common entity. Other etiologies include radiation-induced and post-cardiac injury syndrome.

Often, pericarditis and, specifically, recurrent pericarditis cases will prompt a workup for an autoimmune etiology. More common autoimmune diseases associated with pericarditis include systemic lupus erythematosus, rheumatoid arthritis and systemic sclerosis, although rarely is pericardial involvement implicated as the first clinical presentation of an autoimmune disease.

Autoinflammatory disorders are an emerging cause of acute and recurrent pericarditis. Genetic data links monogenic mutations, such as Mediterranean Fever (MEFV) (implicated in familial Mediterranean fever) and others, including inflammasome-related mutations, to recurrent pericarditis.[22] Concordant with this, a genome-wide association study of almost 5,000 individuals with acute and recurrent pericarditis found an association between pericarditis and sequence variants at the interleukin 1 gene locus.[23] These studies suggest that those with previously presumed idiopathic and/or viral-induced pericarditis may actually hold a genetic predisposition.

Clinical Examination

A comprehensive clinical examination is imperative in the assessment of this patient population and should include assessment for features of:

- Inflammatory pericarditis
- Cardiac tamponade
- Causative etiologies
- Potential alternative diagnoses

Inflammatory pericarditis assessment

A triphasic pericardial friction rub, arising due to friction between the inflamed pericardial layers during cardiac motion, is pathognomonic of inflammatory pericarditis and is a key diagnostic characteristic of this condition. This is typically described as a grating, scratching sound that is heard best at the left sternal border and louder during inspiration.

Although its specificity approaches 100%, its sensitivity is significantly less, occurring in approximately one-third of patients with inflammatory pericarditis.[24] Common findings also include sinus tachycardia and a low-grade fever, although a fever >38°C can be seen in severe inflammatory pericarditis or purulent bacterial pericarditis.

Cardiac tamponade assessment

Patients presenting with inflammatory pericarditis should be carefully assessed for features of cardiac tamponade complicating pericardial inflammation. It should be remembered that the diagnosis of cardiac tamponade is a clinical diagnosis, rather than one made by imaging.

Examination should include assessment for: tachycardia, hypotension, pulsus paradoxus (>10mm Hg decrease in systolic blood pressure with inspiration), jugular venous distention and muffled heart sounds.

Causative etiologies assessment

Clinical examination should include assessment for potential causative etiologies of pericarditis based on the clinical history obtained. This should include a routine comprehensive rheumatologic examination in this patient population to carefully assess for potential autoimmune causes of pericarditis.

Potential alternative diagnoses assessment

Examination should include careful assessment of potential alternative diagnoses that may masquerade as pericarditis, including palpation of the anterior chest wall looking for musculoskeletal tenderness and eliciting epigastric tenderness as a marker for gastritis.

Initial Investigations

Initial investigations in the assessment of inflammatory pericarditis include blood tests, electrocardiography and echocardiography. (*See "Multimodality Imaging" on page 12.*)

Baseline blood tests include assessment of a complete blood count looking for neutrophilic leukocytosis, basic metabolic biochemical panel for baseline assessment of renal function and assessment of inflammatory markers, including erythrocyte sedimentation rate (ESR) and CRP. Given the inflammatory nature of recurrent pericarditis, recurrent flares of chest pain should be associated with elevated inflammatory markers. Normal inflammatory markers in the setting of chest pain should prompt evaluation for alternative nonpericarditic causes of chest pain. Troponin elevation may indicate the coexistent presence of myocardial involvement consistent with myopericarditis.

Based on the history and clinical examination, consideration should be given to additional testing to determine etiology, including auto-antibody panels looking for autoimmune disease and myeloma screening. Viral serologies should not be performed typically given the ubiquitous nature of causative illnesses.

ECG changes occur in approximately 60% of patients presenting with acute pericarditis and suggest coexistent epicardial inflammation. Characteristic ECG changes include widespread concave up ST-segment elevation with PR-segment depression. Typical ECG findings Stage 1, seen in the first hours to days, are characterized by widespread ST elevation (typically concave up) with reciprocal ST depression in leads aVR and V1. These ECG changes evolve with subsequent ST segments normalization with T wave flattening, followed by diffuse T-wave inversions; and, finally, ECG normalization.[25]

Echocardiography may identify a pericardial effusion, which is typically small, in up to 60% of patients. Additionally, it offers assessment for imaging evidence of cardiac tamponade, which may complicate this condition.

CMR offers an additional useful tool in the assessment of inflammatory pericarditis by allowing assessment of pericardial thickness, pericardial delayed gadolinium enhancement and pericardial edema. It is essential that CMR is read by experts in pericardial assessment, as it is not infrequent for epicardial fat to inadvertently be misdiagnosed as delayed gadolinium enhancement of the pericardium. Additionally, it is important to note that following an index episode of acute pericarditis, pericardial delayed gadolinium enhancement is slow to resolve and may persist well beyond 12 months. Hence, the presence of delayed gadolinium enhancement of the pericardium should not be misinterpreted as representing acute pericardial inflammation in the absence of other clinical findings or elevated inflammatory markers.

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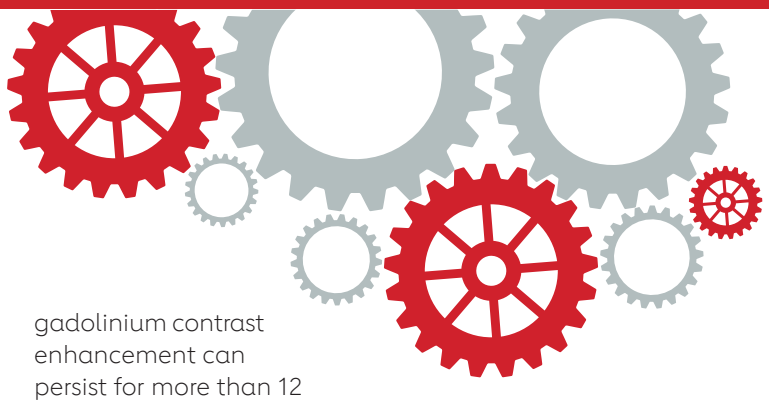


Multimodality Imaging

Echocardiography remains the primary modality for investigating patients with suspected acute pericarditis.[26,27] It can be used to detect a new or worsening pericardial effusion — one of the principal clinical diagnostic features of acute pericarditis.[26,28] Pericardial effusions are typically small and reported to occur in up to 60% of those patients with acute pericarditis.[38] Detailed evaluation for echocardiographic features of cardiac tamponade is warranted regardless of pericardial effusion size. Echocardiographic features of cardiac tamponade include cardiac chamber compression, respirophasic ventricular interdependence, expiratory hepatic venous diastolic flow reversals, exaggerated respirophasic variation in mitral and tricuspid Doppler inflow patterns, and a dilated inferior vena cava consistent with an elevated central venous pressure. Effusive-constrictive pericardial physiology may be demonstrated by echocardiography in patients with severe pericardial inflammation with associated pericardial edema. It can also be used to help evaluate the hemodynamic effects of any effusion and can play a role in the differential diagnosis of chest pain, identifying potential alternative causes (e.g., a new regional wall motion abnormality pointing toward an acute coronary syndrome, or LV dysfunction suggesting a concomitant myocardial pathology).[26]

Cardiovascular magnetic resonance can play an important role in confirming the presence of acute pericarditis, particularly where the history may be atypical or if a patient with a history of pericarditis presents with chest pain but normal inflammatory markers.[26,28] Where the rate of resorption of pericardial fluid matches the rate of production, an effusion may not develop, obscuring the presence of pericarditis on echocardiography.[29] The healthy pericardium is a relatively avascular structure and therefore does not take up gadolinium contrast.[29] However, in the setting of acute pericarditis, there is often neovascularization of the inflamed pericardium and increased pericardial water content due to capillary leak and pericardial edema. The latter can be detected on high resolution T2-weighted turbo spin echo sequences as pericardial T2 hyperintensity.[29] For the same reasons, the inflamed pericardium will appear hyper-enhanced in the late phase after administration of gadolinium contrast agents. The absence of these features lowers the probability of acute pericarditis. Delayed gadolinium contrast enhancement can persist for more than 12 months following an acute episode of pericarditis despite symptomatic resolution, as pericardial vascular changes take time to resolve.[30,31] Hence, the presence of mild delayed gadolinium enhancement without T2 hyperintensity may suggest prior pericardial inflammation without ongoing acute pericardial inflammation. CMR should be considered where a patient presents with a troponin rise or evidence of new contractile dysfunction on echo to identify concomitant myocardial inflammation.[32] This is termed myopericarditis where the dominant pathology is pericarditis or peri-myocarditis where there is extensive myocardial inflammation or LV dysfunction, and pericardial involvement is the more peripheral process.[29] In patients at risk of developing constriction, pericardial late gadolinium hyperenhancement may identify a subset of patients where this may be aborted by appropriate anti-inflammatory therapy.[33]

Cardiovascular computed tomography may be valuable again in the differential diagnosis of chest pain in the setting of suspected pericarditis, e.g., acute aortic syndromes.[26,29] Pericardial inflammation may manifest as pericardial thickening or hyperenhancement post-contrast. Cardiovascular CT should also be considered where there is a history of thoracic trauma, of if concomitant pleuropulmonary pathology or neoplastic cause for pericarditis is suspected.[29] In patients with chronic pericardial constriction, cardiovascular CT may be of value in delineating areas of pericardial calcification as well as ruling out concomitant bystander coronary disease, which may require revascularization at the time of cardiothoracic surgery.

Cardiovascular and wider whole-body fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging may be of value in patients with suspected systemic autoimmune rheumatic disease or where there is concern about internal malignancy as a cause for acute pericarditis.[29] As well as confirming inflammation and assessing disease activity, this may also identify lymph nodes or other structures to target for biopsy where histologic data is lacking.

Introduction to the Immune System, Inflammation and Mechanisms of Drug Action

The immune system plays an important role in defending the body from infectious agents/pathogens, responding to foreign/toxic material and removing abnormal potentially pre-cancerous damaged host cells (cancer surveillance).[34]

The immune system is divided into two main components: the adaptive immune system and the innate immune system. Each plays a crucial role in defending the body against pathogens.

The innate immune response refers in part to the system of proteins and phagocytic cells that are designed to recognize (using pattern recognition receptors) highly conserved molecular signatures that are unique to but common among a range of pathogens, toxins or damaged cells.[35] This can include, for example, toll-like receptor proteins that recognize pathogen associated molecular patterns, such as bacterial lipopolysaccharide.[36] Another group of such proteins that act within the cell to detect pathogens or cell injury are the nucleotide-binding oligomerization domain leucine-rich repeat proteins or NLR — recognizing damage/danger-associated molecular patterns.[37]

When activated, one such protein, called pyrin-containing domain-3 (P3), combines with other cell proteins to form an enzyme complex called an (NLRP3) inflammasome. This contains a cysteine proteinase called caspase-1 (also called interleukin-1 [IL-1] converting enzyme) that is activated by the inflammasome and converts inactive pro-IL-1β to its active form, interleukin-1 beta (IL-1β).[37,38] The latter is a key pro-inflammatory cytokine that orchestrates an ongoing inflammatory response. NLRP3 is an important inflammasome as it responds to a variety of markers of cell injury or stress, and thereby plays a key role in activating an inflammatory response.[38,39]

The adaptive immune response involves cells from the immune system recognizing specific antigens, learning to generate specific antibodies to these, or developing specific cell-mediated immunity to pathogens, damaged and infected cells.[34]

This adaptive process takes time to develop but provides a highly specific targeted response to antigens while minimizing injury to nontarget host cells or tissues.

It also requires tolerance to develop to healthy host cells and tissues.[34] For an antigen the immune system has not encountered before, this process can take at least a week. This is the rationale behind vaccinations, which prime the immune system with the anticipated antigen to accelerate an anamnestic response to the antigen should it be encountered again.

If this were the only component of the immune response, potential pathogens would have a significant time advantage over the host, rendering the host undefended and vulnerable to infection. Until adaptive immunity develops, the host relies on the innate immune response.[17]

Autoimmune disease results from the inappropriate activation of the adaptive immune system by self- or autoantigens.[40] In contrast, the term autoinflammation is used to describe the inappropriate activation and dysregulation of the innate immune response.[40] Although acute pericarditis can occur as a complication of a systemic autoimmune disease such as SLE, most cases of idiopathic or presumed viral pericarditis are thought to have a predominantly autoinflammatory basis.[41] In reality, most conditions with an immunologic basis do not have a pure autoinflammatory or autoimmune basis, but exist on a continuum with varying contributions of dysregulation of both arms of the immune system, which do not exist in isolation.[42]

The drugs used to treat pericarditis target different aspects of the inflammatory cascade.

Colchicine is thought to inhibit the assembly of the NLRP3 inflammasome and so indirectly reduce the production of IL-1β.[43] One action of IL-1β is to stimulate the production of arachidonic acid by the enzyme lipoxygenase.[44] Arachidonic acid in turn is metabolized by the enzyme cyclooxygenase 2 (COX-2) to produce pro-inflammatory prostaglandins.[44]

Nonsteroidal anti-inflammatory drugs, such as ibuprofen and aspirin, work by inhibiting cyclooxygenase.

Corticosteroids have more pleiotropic effects, including inhibition of the transcription of pro-inflammatory genes including those for IL-1 precursors.[45]

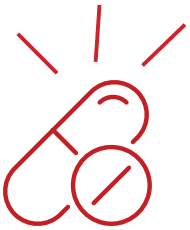
Management of Acute Pericarditis

First-line treatment of acute pericarditis includes off-label use of aspirin or a nonsteroidal anti-inflammatory drug (NSAID) plus colchicine for inflammation, often with a proton pump inhibitor for gastric protection.

Aspirin/NSAIDs

NSAIDs and aspirin inhibit cyclooxygenase and thereby prevent the production of prostaglandins via the metabolism of arachidonic acid. Relatively higher doses of aspirin/NSAIDs are necessary to mitigate symptoms attributed to pericardial inflammation.[46] Aspirin may be used instead of other NSAIDs if the patient is already receiving aspirin for another condition, such as coronary or peripheral artery disease where an antiplatelet effect is required. Acute pericarditis may fail to settle or appear incessant if inadequate doses of NSAIDs are used or if these are stopped abruptly or tapered before symptoms have settled and/or inflammatory markers have normalized. Although other NSAIDs can be used, ibuprofen and aspirin have the advantage that they are inexpensive, readily available and come in tablet dose denominations that greatly facilitate tapering.

NSAIDs are contraindicated when creatinine clearance is less than 30 ml/min, or there is an allergy to NSAIDs or a history of associated asthma exacerbation, recent gastrointestinal ulcer or high risk of bleeding due to concomitant use of anticoagulants. NSAIDs are also contraindicated in patients with a history of acute coronary syndromes, heart failure and in pregnancy at 20 weeks or later.[1,47]



Significant drug interactions with colchicine

Cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) inhibitors can substantially increase serum colchicine concentrations, increasing toxicity.[48] Renal and hepatic impairment further increases this risk. Awareness and risk mitigation strategies should be followed when using these drugs concomitantly. However, concomitant use of strong CYP3A4 and P-gp inhibitors should be avoided, particularly with renal or hepatic impairment.

Common interactions are listed in Table 2. Visit **https://link.springer.com/article/10.1007/s40264-022-01265-1/tables/4** for more information.

Table 1: Treatment and tapering of initial therapies for acute and recurrent pericarditis. [46,48]	Recommended treatment dosing	Duration*		Tapering recommendations
		Acute idiopathic pericarditis (initial episode)	Recurrent pericarditis	
Aspirin	750-1000 mg by mouth every 8 hours	1-2 weeks	Weeks to months	250-500 mg every 1 to 2 weeks
Ibuprofen	600-800 mg by mouth every 8 hours			200-400 mg every 1 to 2 weeks
Colchicine†	0.5-0.6 mg PO twice daily (once daily if <70 kg, age >70 years or intolerant to twice daily dosing)	3 months	At least 6 months	None required

*Duration may vary based on symptoms and time to normalization of high-sensitivity C-reactive protein (<1 mg/L).

†Renal dose adjustments are required, and presence of CYP3A4/P-glycoprotein drug interactions further influences clearance and may preclude safe use of colchicine. A single loading dose of 1-2 mg may be considered before maintenance dosing, but is not necessary and may negatively impact tolerance and adherence.

Colchicine

Colchicine binds to tubulin and inhibits its polymerization into microtubules, which consequently, decreases migration and phagocytosis of leukocytes. Colchicine also blocks the NLRP3 inflammasome complex, and thereby prevents the secretion of the key pro-inflammatory cytokines interleukin-1β and interleukin-18.[48] As an adjunct to an NSAID or aspirin for acute pericarditis, colchicine therapy not only increases the remission rate at seven days, but decreases the chances of incessant or recurrent pericarditis by about 50% with a number needed to treat (NNT) of four.[49] Recurrence is one of the most important complications of acute pericarditis. The role of colchicine and the need to continue this for three months regardless of symptoms should be clearly explained to patients to promote adherence and reduce the risks of patients stopping treatment prematurely when they start to feel better/improve.

Colchicine has a long half-life, so at the end of a course, it can be stopped abruptly without the need for tapering. It is often prescribed twice daily, but if required to promote adherence, the total dose can be given once daily, assuming patient stability and no adverse effects, e.g., 0.5-0.6 mg twice daily can be taken as 1.0-1.2 mg once daily.[50]

Although colchicine is safe when used and dosed appropriately, it has a narrow therapeutic index, and dose adjustment is necessary for renal and hepatic impairment to

Table 2: Significant drug interactions with colchicine.	CYP3A4 inhibitor	P-gp inhibitor	Clinical considerations
Cardiovascular drugs			
amiodarone	X	X	Avoid if possible. If agent must be used, consider colchicine dose reduction and monitor closely.
dronedarone	X	X	Avoid if possible. If agent must be used, consider colchicine dose reduction and monitor closely.
nondihydropyridine calcium channel blockers (diltiazem, verapamil)	X	X	Avoid if possible. If agent must be used, consider colchicine dose reduction and monitor closely.
Macrolide antibiotics			
azithromycin		X	Assess risk/monitor for colchicine toxicity.
clarithromycin	X	X	Avoid combination.
Azole antifungals			
itraconazole	X	X	Avoid if possible. If agent must be used, consider colchicine dose reduction and monitor closely.
ketoconazole	X	X	Avoid if possible. If agent must be used, consider colchicine dose reduction and monitor closely.
fluconazole	X		Assess risk/monitor for colchicine toxicity.
voriconazole	X		Assess risk/monitor for colchicine toxicity.
Antiretrovirals			
protease inhibitors (atazanavir, darunavir, ritonavir) with or without cobicistat	X	X	Avoid combination.
Calcineurin inhibitors			
cyclosporine	X	X	Avoid if possible. If agent must be used, consider colchicine dose reduction and monitor closely.
tacrolimus		X	Assess risk/monitor for colchicine toxicity. Consider colchicine dose reduction.

Clinical considerations provided do NOT take into account impaired renal/hepatic function. This table does not include all possible colchicine drug interactions and is not intended to supplant clinical judgment. Recommendations also vary based on manufacturer package insert and colchicine treatment indication.

prevent toxicity. (*See Table 1. Treatment and Tapering of Initial Therapies for Acute and Recurrent Pericarditis on page 14.*) Furthermore, colchicine is metabolized by CYP3A4 and is also a substrate of P-glycoprotein, which consequently increases the risk for significant drug-drug interactions. Concomitant use of colchicine with strong CYP3A4 or P-glycoprotein inhibitors should be avoided, and close monitoring for colchicine toxicity is warranted with concomitant use of moderate CYP3A4 inhibitors.[51] *(See Table 2 on page 15.)*

Particular caution should be exercised in patients receiving drugs that affect both CYP3A4 and P-glycoprotein. The most common adverse reactions of colchicine are gastrointestinal effects. Colchicine commonly causes diarrhea, and occasionally nausea and vomiting.[52]

If patients experience diarrhea that is likely to be attributable to colchicine, given the benefits, the dose should be halved in the first instance, rather than discontinued. Colchicine can also cause an acquired lactose intolerance that may contribute to diarrhea. Therefore, in addition to reducing the colchicine dose, a lactose-free diet should be attempted.[53] Consider signposting patients to information about lactose-free diets.[54] Proton pump inhibitors can also occasionally contribute to diarrhea. If these are used, consider the need for these and/or switch to a histamine type-2 receptor (H2)-antagonist.

Side effects of colchicine that are less common but serious, and thus require close monitoring and possible dose reduction or discontinuation of the drug, include bone marrow suppression, renal or hepatic impairment, and neuromuscular toxicity. Extra caution is necessary in the elderly, who are at increased risk for neuromuscular toxicity and rhabdomyolysis.[55]

Colchicine is contraindicated in end-stage renal failure (creatinine clearance <15 mL/min), severe hepatic impairment and blood dyscrasias. Although there are varying recommendations based on different product package inserts and indications, the use of colchicine in patients with severe renal impairment is not well-studied. Patients with chronic kidney disease who are also receiving colchicine should be closely monitored for adverse effects. Colchicine is generally avoided in dialysis because it is not removed by dialysis. Avoidance with strong P-glycoprotein inhibitors or CYP3A4 inhibitors should also be strongly considered. Although colchicine crosses the placenta and is generally avoided during pregnancy, it has not been associated with increased fetal malformations when used for familial Mediterranean fever.[56,57,58]

Table 3: Inducers of CYP3A4 and P-glycoprotein.	**CYP3A4 inducer**	**P-gp inducer**
barbiturates	X	
bosentan	X	
carbamazepine	X	X
phenytoin	X	
rifabutin	X	
rifampin	X	X
rifapentine	X	

Concomitant therapy with colchicine may increase rate of colchicine metabolism and decrease plasma concentrations. Avoid if possible.

Muscle toxicity and rhabdomyolysis with colchicine and HMG-CoA reductase inhibitors

Both colchicine and HMG-CoA reductase inhibitors (statins) can cause myotoxicity through unique mechanisms.[59] In addition to colchicine being a substrate for both CYP3A4 and P-gp, select statins are also metabolized by CYP3A4 or eliminated through P-gp, which lends to more multiple interactions between CYP3A4/P-gp inhibitors. Consequently, their coadministration poses an even greater risk for rhabdomyolysis, and data suggests this may become life-threatening.

If there is an indication for concomitant statin therapy, hydrophilic statins such as pravastatin or rosuvastatin should be used to mitigate this risk. Other risk factors for myopathies should be assessed (e.g., renal/hepatic impairment, CYP3A4/P-gp inhibitors). Consider lowering the statin dose and monitoring creatine kinase after two weeks of concomitant colchicine therapy. Visit **https://www.ahajournals.org/doi/10.1161/ATVBAHA.124.319851** for more information.[46,65,66,67,68]

Corticosteroids

For most patients, glucocorticoids should be avoided, if possible, as a first-line therapy for acute pericarditis. Although initially they can provide quick relief of symptoms, they may reduce the efficacy of colchicine, and they have been associated with increased rates of recurrent pericarditis. However, glucocorticoids may be considered if a patient does not respond to effective doses of NSAIDs, and they are used first-line when there

is an underlying systemic autoimmune rheumatic disease or a contraindication to NSAIDs. Where not contraindicated, colchicine should be co-prescribed with prednisone.[1,55]

Glucocorticoids may reduce the efficacy of colchicine, and they have been associated with increased rates of recurrent pericarditis.

Prednisone prescribed at a dose of 0.2-0.5 mg/kg/day for up to four weeks is required before slow tapering is begun, assuming symptoms have resolved, and inflammatory markers have normalized. Doses higher than this can increase the risks of adverse effects without any gain in efficacy. The risk of recurrence is highest when doses are tapered to below 12.5-15 mg, and therefore, tapering below this should be slow.[60] Where not contraindicated, colchicine should be co-prescribed with prednisone and should be stopped only after steroids have been tapered off or at three months, whichever is longer. Patients receiving a prolonged course of oral corticosteroids should be warned about the risks of adrenal suppression and given advice on sick day rules, should they develop any intercurrent illness that prevents them taking and/or adequately absorbing their prednisone.

Before initiating oral corticosteroids, consider checking a baseline hemoglobin A1c (HbA1c), vitamin D and parathyroid hormone (PTH) to ensure patients are vitamin D replete and to guide calcium/vitamin D supplementation to mitigate any impact on bone density. Use the opportunity to promote other lifestyle changes that may reduce risks, such as moderating alcohol intake and smoking cessation. In high-risk patients, consider the need for bone densitometry and formal bone protection. If a patient is exposed to prolonged courses of oral corticosteroids, once a dose of 4-5 mg is reached, it may be necessary to check adrenal reserve with a 9 a.m. cortisol (taken before 10 a.m. and before dosing with prednisone on that day). Where this is insufficient, consider the need for a Synacthen test (ACTH stimulation test) to guide further tapering.[61,62,63]

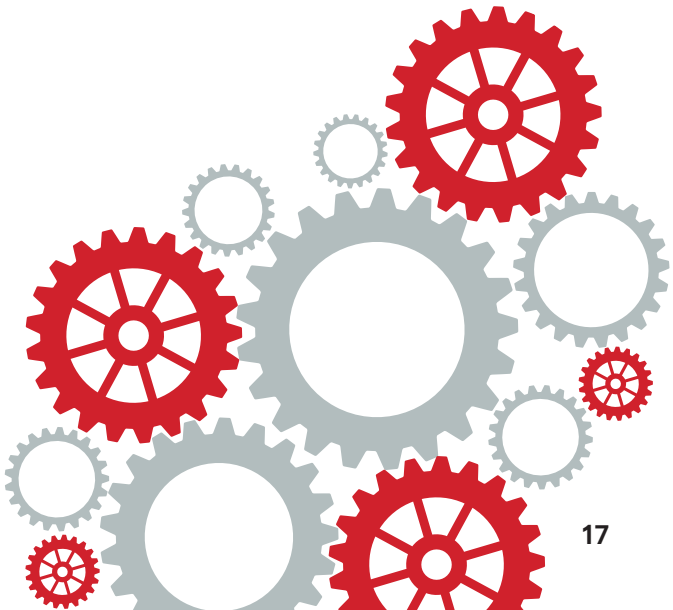
Table 4: Guidance on corticosteroid therapy.[46]

Treatment dose: prednisone 0.2-0.5 mg/kg/day*	
Prednisone dose	**Tapering based on initial treatment dose**
More than 50 mg	10 mg/day every 1-2 weeks
25-50 mg	5-10 mg/day every 1-2 weeks
15-25 mg	2.5 mg/day every 2-4 weeks
Less than 15 mg	1.5-2.5 mg/day every 2-6 weeks
*prednisone 5 mg = prednisolone 5 mg = methylprednisolone 4 mg = dexamethasone 0.75 mg = hydrocortisone 20 mg	

General approach to tapering

Although clinical practice guidelines have defined durations of therapy for acute pericarditis, tapering should only occur if patients are asymptomatic with normalized high-sensitivity C-reactive protein (hs-CRP). Prolonged treatment courses are warranted in persistently symptomatic patients or if hs-CRP remains elevated.

Persistent elevation in hs-CRP concentrations (>3 mg/L) after one week is an independent risk factor for recurrent pericarditis.[64] Hs-CRP should be monitored at baseline and one week after starting therapy to ensure resolution and to help guide therapy. Once symptoms have resolved and hs-CRP has normalized (<1mg/L), tapering of aspirin/NSAIDs and/or corticosteroids can begin.



Lifestyle changes

Physical activity can contribute to the pathophysiology of pericarditis through various proposed mechanisms. Exercise may worsen inflammation through increased oxidative stress and shear stress within the pericardium. Increased blood flow can also elevate the concentrations of circulating antigens.[65]

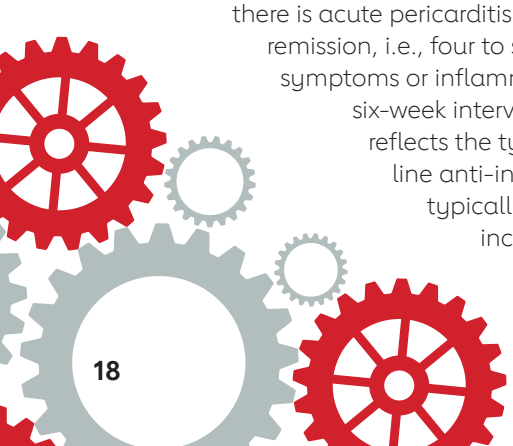
Patients who are not athletes should be advised to avoid exercise and strenuous activities until symptoms resolve and hs-CRP normalizes.

It is recommended that patients who are **athletes** adhere to a more prescriptive three months of exercise restriction and refrain from all competitive sports during this time.

In cases of myopericarditis, both athletes and nonathletes should limit physical activity to low-intensity or normal sedentary activities for three to six months. Reassessment of pericardial effusion should also be conducted before returning to exercise.[66]

Incessant pericarditis

This term is used to describe pericarditis lasting more than four to six weeks but less than three months (at which point the term chronic pericarditis is used).[1] It is also used if there is a symptom-free period of only less than four to six weeks, which is the interval traditionally used to define remission. The term "recurrence" is reserved for circumstances in which there is acute pericarditis after a period of remission, i.e., four to six weeks without symptoms or inflammation. The four- to six-week interval cited is arbitrary but reflects the typical duration of first-line anti-inflammatory treatment, typically with NSAIDs, including tapering.



Common causes of apparently incessant or pseudo-incessant disease include:

Inadequate initial control of inflammation, either through under-dosing of NSAIDs or abrupt cessation of therapy without a taper, or tapering purely based on duration of treatment rather than guided by symptoms/inflammatory markers. (*See "Management of Acute Pericarditis" on page 14.*)

The failure to initiate colchicine or continue this for 3 months following apparent resolution may be another apparent cause. The use of colchicine can potentially halve the risk of recurrence and can also accelerate the attainment of remission when used with NSAIDs.

Although often very effective at rapidly controlling inflammation and symptoms, the early use of corticosteroids in lieu of NSAIDs can also result in recrudescence of symptoms, particularly if tapering is too abrupt or rapid, often with a threshold dose at which recurrence can occur. This risk can be reduced through slow and gradual tapering, particularly at a daily dose of about 12.5-15 mg prednisone (or equivalent).

Finally, another common cause of apparent recurrence may be exercise. Increased cardiac motion and friction within the pericardial sac in conjunction with heart rate and cardiac contractility in response to physical activity may promote recrudescence of inflammation.

An incessant disease trajectory has been reported to occur in up to

12% of patients

presenting to a tertiary pericardial service.[67]

Truly incessant disease, which fails to respond to initial therapy despite adequate dosing, appropriate tapering, adjunctive use of colchicine and avoidance of additional

precipitants of rekindled inflammation such as exercise, may be a harbinger for a more complicated clinical course.[67]

There may be an increased frequency of pericardial complications such as constriction, a phenomenon that is rarely seen in acute idiopathic (presumed viral) pericarditis or recurrent pericarditis. An incessant disease trajectory has been reported to occur in up to 12% of patients presenting to a tertiary pericardial service.[67]

The evidence base for managing these patients is limited. However, incessant disease may prompt the need for more exhaustive investigations for:

- An underlying etiology to the pericarditis
- Treatment of any underlying cause identified
- Escalation of the intensity and duration of anti-inflammatory therapies
- Heightened surveillance for constriction.

Multimodality imaging and particularly CMR may play a role in identifying potentially reversible constriction by delineating ongoing inflammation, which has the potential to respond to immunosuppression.

Assuming an infectious bacterial etiology has been excluded, approaches to inducing remission include:

- The addition of corticosteroids
- The use of higher doses of colchicine (typically increased by 500-600 mcg a day at no less than weekly intervals titrated to response up to a maximum of 3 mg per day, assuming tolerated and no relevant contraindications/drug interactions/ impairment of hepatic or renal drug clearance)
- The use of intravenous immunoglobulin (IVIG) or IL-1 pathway inhibitors. (*See "Recurrent Pericarditis" on page 20.*)

Notes:

Recurrent Pericarditis

Therapeutic options for recurrent pericarditis vary by region. The recommendations in this toolkit are based on the 2025 ESC guidelines. Clinicians should follow current evidence and locally available therapies.

Overview and epidemiology

Recurrent pericarditis is defined, according to the 2025 ESC guidelines, as new symptoms or disease activity following clinical remission. This typically occurs after a documented first episode of acute pericarditis, a symptom-free interval, complete discontinuation of anti-inflammatory therapy and subsequent recurrence of pericarditis, usually within 18 months of the index episode.[14] Recurrence occurs in about 20–30% of patients within 18 months after a first episode of acute pericarditis and up to 50% after a first recurrence.[68,69] Corticosteroid use (especially long-term use or doses above 1 mg/kg/day), lack of response to anti-inflammatories and persistent elevations in hsCRP are independent risk factors for recurrence.[70]

Therapeutic options for recurrent pericarditis differ between regions. In the United States, rilonacept is currently the only IL-1 pathway inhibitor approved by the FDA for this indication, whereas no IL-1 pathway inhibitors have received EMA approval in Europe. The recommendations outlined below reflect the 2025 ESC Guidelines, which is the only published guideline on pericarditis management. Clinicians should adhere to best practices based on current evidence and the therapeutics available in their region.

Recurrent pericarditis is an autoinflammatory disease which results in activation of the inflammatory cascade mediated by interleukin-1 and other cytokines, which can last for years, characterized by multiple recurrences. The median duration of disease in patients with two or more recurrences is three years, with ~35% of patients still suffering at five years and ~25% at eight years.[5] These findings were affirmed by a multicenter, longitudinal study with longest follow-up showing a median disease of 3.8 years.[71]

Pharmacologic management

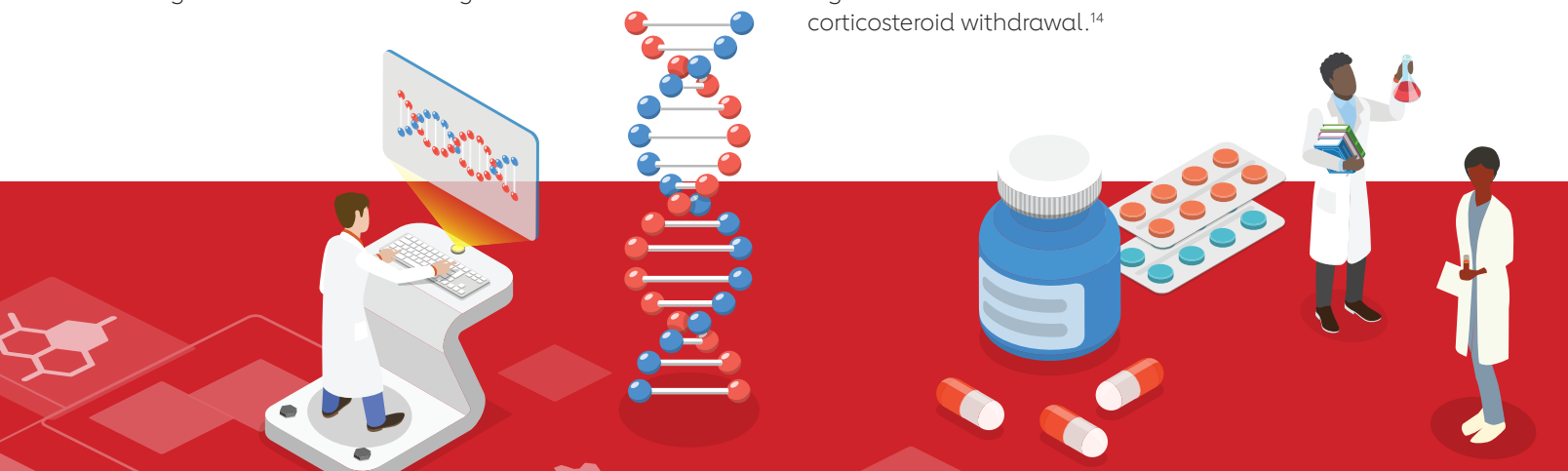
Initial therapy:

Initial therapy for the first recurrence of pericarditis is similar to that of the first episode of acute pericarditis but with longer durations of therapy. (*See Table 1: Treatment and tapering of initial therapies for acute and recurrent pericarditis on page 14.*) For recurrent pericarditis, aspirin/NSAID therapy lasts weeks to months, while colchicine therapy should be continued for at least six months. Combination therapy with aspirin/NSAIDs plus colchicine for recurrent pericarditis has been shown to significantly reduce further recurrence compared to standard therapy, with an absolute risk reduction of 26.6% at 18 months.[72]

Subsequent therapy:

Over the past decade, IL-1 pathway inhibition has emerged as a therapeutic strategy for patients with multiple recurrences of pericarditis. Earlier expert opinions and the 2025 ACC Concise Clinical Guidance (CCG) position IL-1 pathway inhibitors (e.g., rilonacept — the only FDA-approved treatment for recurrent pericarditis — or anakinra) as second-line monotherapy in patients failing NSAIDs and colchicine ahead of or instead of corticosteroids.[73]

The 2025 ESC Guidelines provide more nuanced recommendations. It recommends anti-IL-1 therapy for patients with recurrent pericarditis who have failed first-line therapies and corticosteroids and who show elevated C-reactive protein (CRP) levels to reduce recurrences and allow corticosteroid withdrawal (Class I). IL-1 blockade may also be considered in cases of failure, contraindications and intolerance to first-line therapies and corticosteroids regardless of CRP levels to reduce recurrences and allow corticosteroid withdrawal.[14]



This approach reflects a shift toward personalized, inflammation-targeted therapy and accounts for regional differences in available therapies, rather than a universal second-line strategy. Clinicians should adhere to best practices based on current evidence and the therapeutics available in their region.

Low- to medium-dose corticosteroids plus colchicine, or triple medical therapy with corticosteroids, NSAIDs and colchicine, should be considered for patients with pericarditis only in case of contraindication/failure of aspirin/NSAIDS and colchicine (Class IIa). However, patients may experience pericarditis recurrences as a consequence of serial tapering to mitigate the risk of iatrogenic consequences, resulting in periodic sub-therapeutic dosing and subsequent unmasking of the underlying disease.

Long-term management of recurrent pericarditis with corticosteroids is associated with an increased risk of adverse effects. These may include immunosuppression, osteoporosis, weight gain, hyperglycemia, hypertension, fluid retention, gastrointestinal upset, adrenal suppression and mood changes.[74] Therefore, minimizing prolonged corticosteroid exposure is a key therapeutic goal in managing patients with recurrent disease.

Role of interleukin-1

In recurrent pericarditis, patients mount an abnormal innate inflammatory system response, which is mediated primarily by the IL-1 pathway and other cytokines. The two main isoforms of IL-1 pathway are IL-1α and IL-1β. Both isoforms exert their effects via the IL-1 receptor. Of the two, IL-1β is the more predominant isoform and contributes significantly to the pathophysiology of the pericarditis flare. Activation of the NLRP3 inflammasome, which can be initiated by IL-1α, stimulates the production of active IL-1β, which can then promote the activation of COX-2.[75]

IL-1α and β bind to IL-1 receptor type 1 on the pericardium and stimulate additional IL-1α and β, thereby creating a self-perpetuating cycle of autoinflammation. IL-1 pathway inhibitors not only rapidly reduce symptoms and signs of inflammation but also provide a corticosteroid sparing effect that allows patients to be tapered off corticosteroids safely without disease relapse, especially in the setting of multiple recurrences and persistently elevated CRP, or in second-line treatment, obviate the need to initiate steroids. The two main agents used in recurrent pericarditis that directly target IL-1 are anakinra and rilonacept.

Rilonacept is the first and only FDA-approved treatment for the treatment of recurrent pericarditis and reduction in risk of recurrence in adults and children aged 12 years and older. It is an IL-1 trap protein that serves as a decoy IL-1 receptor that traps IL-1α and β cytokines. In the phase 3 RHAPSODY, 86 patients with a history of at least two recurrences, elevated CRP (≥1 mg/dL) and a pericarditis pain score of at least four were enrolled. All patients received rilonacept treatment for 12 weeks while being weaned off background therapies (run-in period [RI]). Rilonacept resolved or nearly resolved chest pain after only a median of five days and normalized CRP after a median of seven days. Time to rilonacept monotherapy was 7.9 weeks.[77] In the run-in period, 97% of participants achieved a treatment response (NRS score ≤ 2 and CRP ≤ 0.5 mg/dL).

After the 12-week run-in period, patients entered an event-driven randomized withdrawal (RW) period where 61 patients were randomly assigned to weekly rilonacept or placebo. In the RW period, the median time to pericarditis recurrence in the rilonacept arm could not be calculated because there were too few recurrence events; the median time to recurrence in the placebo arm was 8.6 weeks. Rilonacept treatment resulted in a 96% reduction in risk of recurrence (HR 0 .04 [95 % CI, 0.01 to 0.18], P <0.0001). At the time when the event-driven portion of the trial had

closed, two of 30 (7%) patients in the rilonacept group and 23 of 31 (74%) patients in the placebo group experienced a recurrent episode.

In the RHAPSODY long-term extension (LTE), 74 out of 75 eligible patients continued and received open-label rilonacept for up to 24 additional months. For each LTE patient, 18 months after the most recent pericarditis recurrence (qualifying or RW period), a decision was made to continue rilonacept, suspend rilonacept for off-treatment observation or discontinue from LTE. For the patients that continued treatment with rilonacept past the 18-month decision milestone, there was a 98% reduction in risk of recurrence (HR, 0.02; P<0.0001), consistent with the primary efficacy endpoint.

Registry of the natural history of recurrent pericarditis in pediatric and adult patients (RESONANCE) (NCT04687358), the first multicenter U.S. recurrent pericarditis patient registry, launched in March 2021 and is currently ongoing. Data from RESONANCE demonstrate that second-line management of patients failing aspirin/NSAIDs/colchicine has shifted increasingly toward IL-1 pathway inhibition, and the initiation of corticosteroids decreased each year after rilonacept approval in recurrent pericarditis.

Anakinra is a recombinant human IL-1 receptor antagonist (IL-1RA) that competes with endogenous IL-1 and mimics the effects of a native human interleukin-1 receptor antagonist (IL-1RA), blunting the activity of both IL-1α and β. It has been used off-label in the treatment of recurrent pericarditis. The AIRTRIP trial randomized 21 colchicine-resistant, corticosteroid-dependent patients with a history of three or more recurrences. After an open-label phase in which all patients received anakinra for two months, patients were randomized to anakinra or receive placebo. All patients in the two-month, open-label phase experienced a complete response to anakinra after approximately one week of therapy. During the withdrawal phase, recurrence occurred in 18% of patients receiving anakinra versus 90% of those on placebo, meaning approximately 82% of patients on anakinra remained recurrence-free (incidence rate ratio 0.055; P<0.001). Approximately half of the participants remained on colchicine, as monotherapy was not a requirement of the study.[76]

Other therapies

Canakinumab, a monoclonal antibody that binds to IL-1β, can be considered, though evidence of its use in pericarditis is mainly limited to case reports. Goflikicept is a heterodimeric fusion protein that binds to IL-1α and β cytokines with high affinity. It has been investigated in a phase 2 and 3 randomized open-label study in adults with idiopathic recurrent pericarditis. The study consisted of four phases: a four-week screening phase, a 12- or 24-week run-in phase based on background therapies and included 10 weeks of goflikicept monotherapy, a 24-week placebo-controlled randomized withdrawal phase and an eight-week safety follow-up period. Goflikicept was dosed at 80 mg subcutaneously once weekly. During the run-in phase, treatment with goflikicept significantly reduced CRP levels, chest pain and pericardial effusion size. During the randomized withdrawal period, 90% of patients in the placebo group experienced a recurrence compared to no patients in the treatment group.[74] Goflikicept is approved for use only in the Russian Federation.

The most common adverse effect of IL-1 blocking agents is injection site reactions, but these are typically mild and self-limiting, and patients can employ several techniques to mitigate these. (*See "Patient Education Checklist" on page 24.*)

IL-1 blockers are associated with increased risk of infections, most commonly upper respiratory infections; they may blunt inflammatory signs, so infections should be monitored and serious infections prompt treatment interruption.

Duration of therapy and tapering

Decisions around treatment duration should consider the natural history of recurrent pericarditis, including how much of the expected disease course has elapsed. Discontinuation of therapy should be guided by clinical judgment and whether the underlying autoinflammatory process re-emerges upon dose reduction, dose interval elongation or treatment withdrawal. Should symptoms or inflammatory activity re-emerge, prompt re-initiation of therapy is warranted to restore disease control and continue treatment for the duration of the underlying disease course.

Tapering of NSAIDs or corticosteroids is initiated after clinical improvement and CRP normalization, typically within one to two weeks of IL-1 inhibitor initiation.[18] Thereafter, NSAIDs may be withdrawn over the next two weeks and

corticosteroids within six to 10 weeks following IL-1 receptor blocker commencement. Colchicine should be maintained and withdrawn only as the last drug after achieving stable remission. It has the safest cardiovascular profile and is now proposed to help prevent major adverse cardiac events (MACE) in patients with atherosclerotic cardiovascular disease. In patients who achieve stable remission with a chronic low dose of corticosteroids (e.g., prednisone ≤5 mg or equivalent) plus colchicine, the decision to switch to IL-1 blocker therapy should be individualized, taking into account factors such as tolerability, age, sex-related considerations and patient preference.

Assess patients for persistence of disease by suspending treatment. It should be noted that IL-1 receptor blocker therapy discontinuation, while the underlying disease is still present, is associated with a high risk of pericarditis recurrence. In the International Registry of Anakinra for Pericarditis (IRAP), anakinra discontinuation was associated with a 57% risk of recurrence at 36-month follow-up.[79]

Rilonacept[14] FDA-approved*	**Adults** Loading dose: 320 mg (divided into two 160 mg doses administered subcutaneously at different injection sites). Maintenance dose: 160 mg subcutaneously once weekly, starting one week after initial dose. **Pediatric Patients (12 to 17 years old)** Loading dose: 4.4 mg/kg, up to a maximum of 320 mg, delivered as one or two injections (not to exceed 2 mL/injection). Maintenance dose: 2.2 mg/kg subcutaneously, up to a maximum of 160 mg, once weekly.
Anakinra[13]	Dose: 1–2 mg/kg, up to a maximum of 100 mg, subcutaneously every day. Consider dosing every other day in patients with creatinine clearance less than 30 mL/min.

*Rilonacept is the only FDA-approved therapy for the treatment of recurrent pericarditis and reduction in risk of recurrence in adults and pediatric patients 12 years and older.

Time to pericarditis recurrence (approximately two months) after rilonacept suspension without taper is predicted by the gradual washout pharmacokinetics of once-weekly rilonacept. Rilonacept suspension during the long-term extension phase of the RHAPSODY study was associated with a recurrence rate of 75% with a median time to recurrence of 11.8 weeks.[80]

Potential strategies to reduce the risk of pericarditis recurrence following IL-1 receptor blocker discontinuation include longer duration of IL-1 receptor blocker therapy and medication tapering.

In a retrospective review of 17 Italian patients after RHAPSODY completion, approximately 80% experienced a pericarditis recurrence after rilonacept suspension, with median time to recurrence of eight weeks. Potential strategies to reduce the risk of pericarditis recurrence following IL-1 receptor blocker discontinuation include longer duration of IL-1 receptor blocker therapy and medication tapering. Due to a longer elimination half-life (about seven days), RHAPSODY used a simpler paradigm of treatment cessation without tapering, enabled by the gradual washout of rilonacept over approximately eight weeks. In a sub-analysis of RHAPSODY assessing patient-reported outcomes in patients with recurrence, the return of recurrent pericarditis symptoms was gradual, with pain scores increasing in the one- to two-week period prior to a reported event. Reinitiation of rilonacept resulted in the resolution of the acute recurrence in patients where the underlying disease was still present. The effectiveness of changing the FDA-approved interval of rilonacept administration on subsequent pericarditis recurrence risk is unknown.

Potential tapering strategies for anakinra[81]

- Reduce by one administration day per week.
- Reduce to every other day dosing for three months, followed by half dose every other day for one to three months.

Practical Prescribing of IL-1 Blockers[82,83]

Pretreatment monitoring checklist

- ☐ Signs/symptoms of active infection
- ☐ Tuberculosis screening (e.g., skin test, interferon-gamma release assay, recent chest X-ray)
- ☐ Hepatitis B and C serologies
- ☐ Human immunodeficiency virus screening (e.g., rapid antigen/antibody test)
- ☐ Immunization history and anticipated vaccination schedule
- ☐ Complete blood count
- ☐ Renal function (for anakinra)
- ☐ Pregnancy status
- ☐ Active malignancy
- ☐ Active treatment with anti-TNF agents, including:
  - ○ Adalimumab
  - ○ Certolizumab pegol
  - ○ Golimumab
  - ○ Infliximab
  - ○ Etanercept
  - ○ Lenalidomide
  - ○ Pomalidomide

Patient education checklist

- ☐ Refrigeration storage
- ☐ Preparation, reconstitution (rilonacept) and injection techniques
- ☐ Proper dosing and handling of missed doses
- ☐ Common and serious adverse effects
- ☐ Mitigation of injection site reactions, including:
  - ○ Bring medication to room temperature before injection
  - ○ Use cold compress before and after injection
  - ○ Apply topical corticosteroids or antihistamines to injection site
  - ○ Consider using oral antihistamines, if needed
  - ○ Rotate injection sites and avoid bruised or tender areas
- ☐ Signs/symptoms of infection and when to temporarily hold therapy
- ☐ Manage refills and awareness of patient access issues. This includes renewals for prior authorizations or patient assistance programs and providing any necessary documentation.

Kineret. Package insert. Swedish Orphan Biovitrum AB (publ); 2020.
Arcalyst. Package insert. Kiniksa Pharmaceuticals; 2021.

Getting access to IL-1 blockers

Rilonacept is the first and only FDA-approved treatment for the treatment of recurrent pericarditis and reduction in risk of recurrence in adults and children aged 12 years and older. Use of anakinra is off-label, which may lead to additional insurance coverage barriers that must be overcome in order to ensure patient access.

While prior-authorization may be required for on-label use of rilonacept, out-of-pocket costs to the patient can be lowered through co-pay cards and patient assistance programs found on pharmaceutical company websites or through other resources such as NeedyMeds (**www.needymeds.org**). If the patient is unable to afford anakinra or rilonacept, despite all attempts to reduce cost, then azathioprine may be considered.[1]

Surgery for Refractory Disease

Radical surgical pericardiectomy should be considered as potential definitive therapy in patients with refractory symptoms, or where long-term medical therapy (including IL-1 pathway inhibitors) cannot be withdrawn or is contraindicated. Such surgery should be performed at the hands of experienced pericardial surgeons at expert pericardial centers. Performance of a traditional complete pericardiectomy, removing the anterior and inferior pericardium alone, is insufficient for the treatment of recurrent pericarditis. Complete or near-total removal of the pericardium is essential, including removal of posterior pericardium along the left ventricular lateral wall. Surgery may necessitate the use of cardiopulmonary bypass to decompress the heart to allow adequate access for pericardial resection.

In contrast to those patients with constrictive pericarditis, radical surgical pericardiectomy for recurrent pericarditis is associated with low mortality and morbidity.

In a study from Mayo Clinic:

- Radical pericardiectomy for recurrent pericarditis was associated with **no perioperative mortality and a 3% incidence of major postoperative complications**, including one early reoperation for postoperative bleeding and one CVA.[84]
- At a mean follow-up of 5.5 years, surgical pericardiectomy was associated with **91.4% freedom from recurrence as compared with 71.4% in the medical treatment group**.[1]
- Pericardiectomy was associated with **improvement in symptoms and fewer relapses** as compared with those who did not undergo pericardiectomy.[84]

Notes:

Special Topics

Pericarditis and pregnancy

Pericarditis can affect women of reproductive age. Although incidence is not clearly characterized, data suggest it is similar to age-matched controls.[85,86] The most common finding of pericardial disease in pregnancy is a pericardial effusion, which is often asymptomatic and not associated with pericarditis. Most cases of pericarditis are idiopathic in nature, and although similar to the nonpregnant patient, pericarditis may be secondary to autoimmune, autoinflammatory or viral infections.

The diagnostic approach to pericarditis in pregnancy is similar to nonpregnant patients, with some caveats. Pleuritic chest pain is the most common symptom, and patients may experience symptoms such as dyspnea when supine that may be disregarded as a normal symptom of pregnancy.

Diagnostics include the classic physical exam findings, as well as ECG, laboratory data and imaging. ECG changes should be interpreted cautiously and in the clinical context, as healthy pregnant patients can have T-wave changes in second and third trimesters. Additionally, inflammatory markers (hsCRP and ESR) may rise in normal pregnancy. Imaging is an important diagnostic tool with echocardiogram as the first-line imaging modality. In later pregnancy, subcostal views may be limited. Up to 15% of healthy pregnant patients may have a pericardial effusion, in acute pericarditis pericardial effusion has been noted in up to 60%-80% of patients. Advanced imaging is less commonly used, given concerns with gadolinium contrast during pregnancy. Figure 1 on page 27 highlights the challenges associated with pericarditis during pregnancy.

The management of pericarditis requires a thoughtful approach with multidisciplinary collaboration between OB-GYN, cardiology and rheumatology. Treatment recommendations can change depending on the trimester, which are detailed in Table 6 on page 22. It is recommended as a general guidance that patients with prior pericarditis or recurrent pericarditis achieve disease control at least six months prior to conception.

Table 7: Considerations for pharmacologic management of pericarditis before, during and after pregnancy.

	Preconception/ periconception	1st and 2nd trimesters	3rd trimester	Breastfeeding
NSAIDs	Avoid if feasible, may affect ovulation	Use (ibuprofen preferred)	Avoid (except low dose aspirin)	Use
Colchicine	Use	Use	Use	Use
Corticosteroids	Use	Use (prednisone or prednisolone preferred, dose <20mg/day)	Use (nonfluorinated preferred, dose equivalent of <20mg/day prednisone)	Use (nonfluorinated preferred, dose equivalent of <20mg/day prednisone)
IL-1RA	Selective use*	Selective use*	Selective use*	Use (limited data but presumed safe)
Azathioprine	Use	Use	Use	Use
IVIG	Use	Use	Use	Use
Methotrexate	Avoid; discontinue 1-3 months prior	Avoid	Avoid	Avoid
Mycophenolate mofetil	Avoid; discontinue 6 weeks prior	Avoid	Avoid	Consider alternative but reasonable with counseling

Reprinted with permission: Pryor, K et al. Pericarditis Management in Individuals Contemplating Pregnancy, Currently Pregnant, or Breastfeeding. Curr Cardiol *Rep 25, 1103–1111 (2023).*

*There should be shared decision making with the patient by a multidisciplinary care team (e.g., obstetrics, rheumatology, cardiology) of IL-1 inhibition use in pregnancy recognizing that there are no formal society guidelines that recommend the use of IL-1 inhibition in pregnancy.

Safety of medications during pregnancy follows the formal recommendations in the 2020 American College of Rheumatology reproductive health guideline.[87] In general, first-line therapies with NSAIDs and the recommendations will vary based on the trimester, such that should only be used in first or second trimester.

Colchicine, although once considered a teratogen, has accumulating data for safety from diseases that require colchicine (such as familial Mediterranean fever), resulting in societal guidelines that no longer discourage colchicine use during pregnancy and breastfeeding.[87] Glucocorticoids remain second-line, and both the dose and form require consideration during pregnancy. In general doses, less than 20mg/day and ideally <10mg/day are advised.

For refractory disease, IL-1 pathway inhibitors may be conditionally considered although literature remains limited.[88] Other disease-modifying antirheumatic drugs (DMARDs) have less data, but importantly agents such as methotrexate and mycophenolate mofetil (MMF), which may be used in refractory pericarditis, are contraindicated during pregnancy and should be discontinued prior to conception. Azathioprine however is safe in pregnancy.

Figure 1: Challenges of pericarditis in pregnancy.

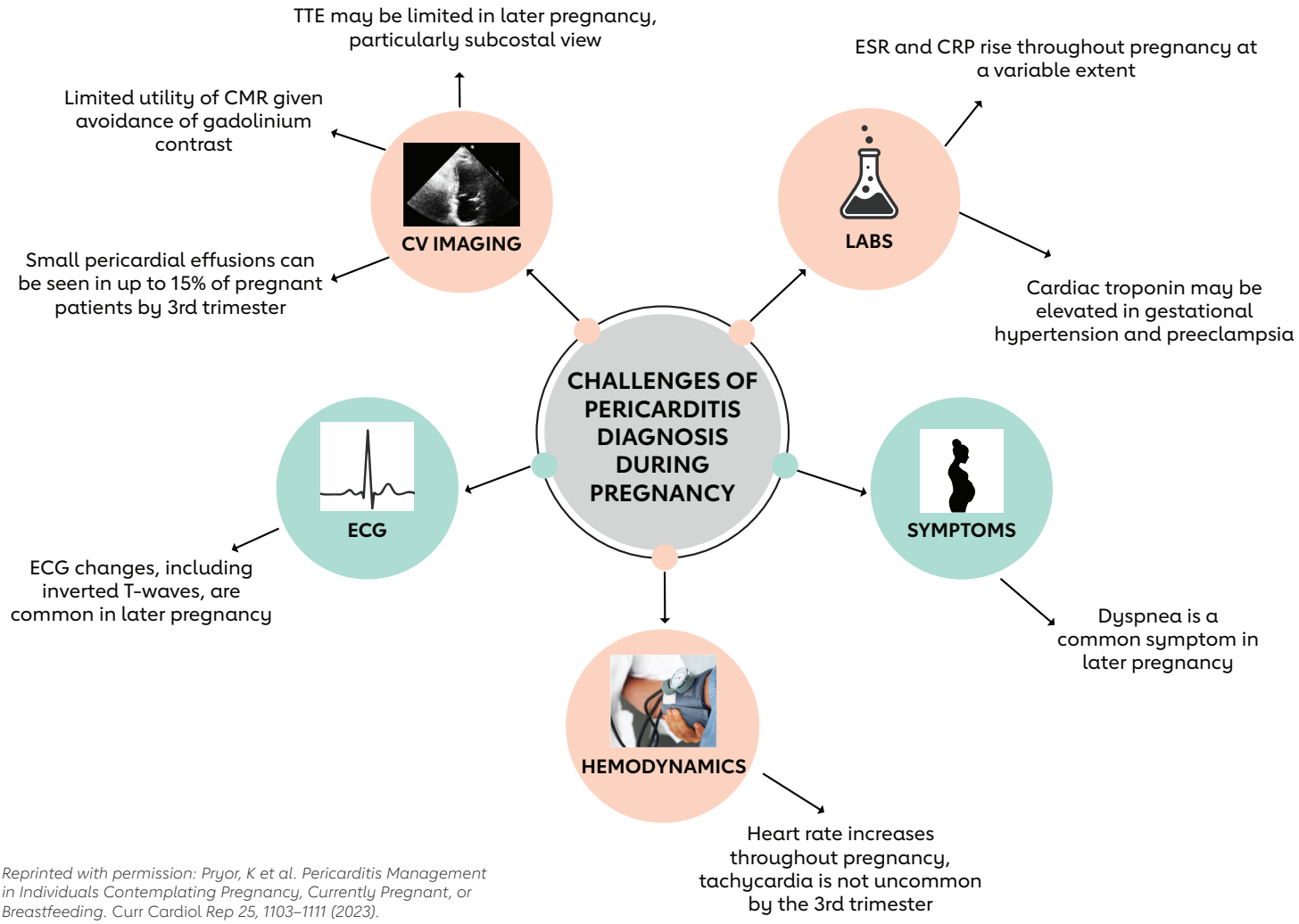


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Table 5: Multimodality Imaging Features of Constrictive Pericarditis.[93]

TTE	CCT	CMR
• Respirophasic ventricular dependence/septal shift • E-wave predominant LV filling with respirophasic variation • Dilated inferior vena cava with <50% collapse • Hepatic vein end-diastolic expiratory reversal flow velocity/forward flow velocity ≥0.8 • Normal or increased medial mitral annular e' velocity (>8 cm/s) • Annulus reversus (medial > lateral e' mitral annular velocity • Loss of superior vena cava systolic flow variation • Respirophasic variation across mitral and tricuspid valve E-wave inflow velocities (>25% and >40%, respectively)	• Increased pericardial thickness • Pericardial calcification	• Increased pericardial thickness • Respirophasic ventricular dependence on free breathing cine white-blood sequences • Wall tethering and conical deformity of the ventricle on cine-white blood and tagging sequences • Inflammation LGE and edema on T2-STIR (in inflammatory TCP)

No single isolated imaging finding is diagnostic of CP; a constellation of findings in conjunction with clinical features of CP is required to make the diagnosis.

CCT = cardiac computed tomography; CMR = cardiac magnetic resonance; CP = constrictive pericarditis; LGE = late gadolinium enhancement; LV = left ventricular; STIR = short tau inversion recovery; TCP = transient constrictive pericarditis; TTE = transthoracic echocardiography.

Adapted with permission from Klein et al.[1]

Constrictive pericarditis

Constrictive pericardial physiology may exist among those with significant pericardial inflammation and edema, resulting in pericardial constraint. Fibrotic constrictive pericarditis is thought to be an infrequent complication of recurrent inflammatory pericarditis. As a result, constrictive pericardial physiology should prompt further evaluation looking for pericardial inflammation, which may be responsive to anti-inflammatory therapy. Although inflammatory markers may have normalized, CMR provides an invaluable tool in the assessment of pericardial inflammation as a potential cause for constrictive pericardial physiology. Careful attention should be paid to the presence of T2-weighted edema sequence hyperenhancement and significant delayed gadolinium enhancement. Where pericardial inflammation is present, an initial trial of anti-inflammatory therapy, including either NSAIDs or corticosteroid or IL-1 receptor blockade, is warranted to determine if therapy results in resolution of constrictive pericardial physiology. In those patients, refractory to medical therapy, surgical pericardiectomy should be considered.

Pericarditis and COVID-19 vaccination

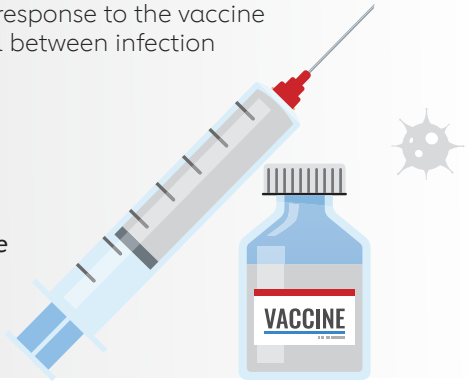
There have been rare reports of myocarditis and pericarditis triggered by vaccination against SARS-CoV-2 with messenger RNA (mRNA)-based vaccines and the Novavax protein-subunit vaccine.[89] Most cases appear to affect boys and young men (age <40 years) within seven days of dosing and typically occur after the second dose.[90] However, a history of pericarditis or myocarditis due to a vaccine unrelated cause does not appear to be associated with an increased risk of this complication. Therefore patients with a history of previous vaccine unrelated pericarditis should be vaccinated as normal, provided they are currently in remission.[89] An episode of pericarditis or myocarditis occurring >3 weeks after vaccination is unlikely to be related.

Although most cases of vaccine-associated myocarditis and pericarditis occur within seven days of exposure, the CDC advises that any case occurring within three weeks should be considered as potentially associated as a precaution.[89] Where it is suspected a case is vaccine-related, current advice is to avoid further dosing. If further dosing is considered, e.g., where it is unclear whether an episode is vaccine-associated, or where the individual is at significantly increased risk of SARS-CoV2-infection and complications or will be immunosuppressed heightening such risks, further dosing should only take place after complete resolution of symptoms and signs pericarditis/myocardial inflammation, and only after a careful individualized risk assessment.[89]

Where a case of pericarditis is thought to be due to SARS-CoV2 infection itself, vaccination should only be considered after full recovery and should be deferred for 90 days post-symptom onset or testing positive based on:

- Low likelihood of reinfection within the 90-day window.
- Likely better immune response to the vaccine with increased interval between infection and vaccination.[89]

As this is an area of evolving evidence, all practitioners should consult the CDC website for the latest guidance and advice for all scenarios.



Top Takeaways

1. Careful clinical evaluation is essential to confirm the diagnosis of recurrent pericarditis. Further evaluation for alternative non-pericardial causes of chest pain should be performed where patients present with acute chest pain without coexistent elevated inflammatory markers (CRP). Beware of mimickers including particularly musculoskeletal chest pain, gastroesophageal reflux disease and fibromyalgia.

2. The mainstay of therapy for an initial acute pericarditis episode is aspirin/NSAIDs plus colchicine and exercise restriction.

3. Low-dose corticosteroids should be reserved for patients who cannot tolerate first-line therapies or as add-on to first-line therapies in recurrent pericarditis if aspirin/NSAIDs and colchicine fails.

4. Rilonacept (FDA-approved in the U.S.) and anakinra (used off-label) are IL-1 pathway inhibitors recommended in selected patients with recurrent pericarditis after failure of NSAIDs/colchicine or in steroid-dependent cases.*

5. IL-1 receptor blocker discontinuation is associated with a high incidence of pericarditis recurrence due to the underlying disease process that may be present.

6. Radical surgical pericardiectomy, performed at the hands of experienced pericardial surgeons at expert pericardial centers, should be considered in patients with refractory disease or where long-term medical therapy cannot be withdrawn or is contraindicated.

7. Median duration of disease in patients with two or more recurrences is three years. The optimal duration of recurrent pericarditis therapy is not established and should be individualized based on disease activity and recurrence risk.

* *Clinicians should adhere to best practices based on current evidence and the therapeutics available in their region.*

Notes:

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