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Advances in Imaging and Targeted Therapies for Recurrent Pericarditis
A Review

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IMPORTANCE Pericarditis is the most common form of pericardial disease. Recurrence of pericarditis affects 15% to 30% of patients after the initial episode of pericarditis. Up to 50% of patients with the first recurrence have additional recurrences. These patients often progress to have colchicine-resistant and corticosteroid-dependent disease. Rapidly evolving cardiac magnetic resonance imaging techniques and novel targeted therapies have paved the way for imaging-guided therapy for recurrent pericarditis. However, the optimal application of these recent advances remains unclear.

OBSERVATIONS A search was conducted using the PubMed and Cochrane databases for English-language studies, management guidelines, meta-analyses, and review articles published until April 2022 on recurrent pericarditis. Following the 2015 European Society of Cardiology guidelines for the diagnosis and management of pericardial diseases, new clinical trials and registry data have emerged that demonstrate the efficacy of interleukin-1 blockers in recurrent pericarditis. In addition, new observational data have come to light supporting the use of cardiac magnetic resonance imaging in the diagnosis, risk stratification, and management of such patients.

CONCLUSIONS AND RELEVANCE Advances in imaging and targeted therapies have led to a paradigm shift in the management of recurrent pericarditis. This narrative review summarizes the established and emerging data on the diagnosis and treatment of recurrent pericarditis with special emphasis on the role of cardiac magnetic resonance imaging and interleukin-1 blockers in the current era of tailored therapy for recurrent pericarditis.

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Multimedia

Supplemental content

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Case: A 47-year-old female individual presents with sharp pleuritic chest pain radiating to the left shoulder, which improves with leaning forward. About 5 months ago, she had a first episode of acute pericarditis and started taking ibuprofen, 800 mg, 3 times daily and colchicine, 0.6 mg, 2 times daily. Two months later, while receiving therapy, she had a recurrence of chest pain and was found to have a C-reactive protein (CRP) level of 24.4 mg/dL (to convert to milligrams per liter, multiply by 10). She was diagnosed with recurrent pericarditis, and prednisone, 20 mg, once daily was added to her regimen. Three months later, while tapering the prednisone and continuing ibuprofen and colchicine, she presents with sharp chest pain, which she describes as her pericarditis acting up again. What should be the diagnostic and therapeutic approach for this adult with recurrent pericarditis?

Pericarditis accounts for 5.4 to 26 hospitalizations/100 000 persons per year in the US.[1-3] The spectrum of pericarditis ranges from acute pericarditis to various other forms, such as recurrent, incessant, chronic, and constrictive pericarditis. Up to 30% of patients with acute pericarditis experience debilitating recurrent episodes of pericarditis following a short symptom-free period of 4 to 6 weeks; these patients are classified as having recurrent pericarditis.[4] Retrospective studies estimate 37 000 US patients with recurrent pericarditis with an incidence of 6 of 100 000 persons per year.[5] Once the diagnosis of recurrent pericarditis is established, management involves a combination of anti-inflammatory drugs, often leading to steroid dependence in refractory cases.[6] The mean duration of recurrent pericarditis in patients who are difficult to treat can be remarkably long (up to 4.7-6.2 years) from the onset until the complete suspension of therapy adding substantially to morbidity and health care costs.[7,8] The purpose of this review is to guide clinicians on the current diagnostic and therapeutic approach for recurrent pericarditis with emphasis on what is new since the 2015 European Society of Cardiology (ESC) guidelines.

Etiology

In low-resource countries, tuberculosis is the leading cause of pericarditis.[9] In high-resource countries, up to 90% of cases of pericarditis are idiopathic and assumed to be viral in origin.[10,11] Postcardiac injury syndromes are emerging causes of pericarditis, given the increased number of percutaneous coronary interventions, coronary artery bypass grafting, transcatheter valve repair/replacements, and electrophysiology procedures.[12,13] Other noninfectious causes include hypothyroidism, malignant neoplasms, autoimmune diseases, and radiotherapy.[6] The 2015 ESC guidelines

recommend etiologic search only in (1) suspected tuberculosis, (2) patients with a clinical presentation suggesting a particular etiology, such as systemic inflammatory disease, or (3) patients with risk factors for poor prognosis, such as the absence of response to nonsteroidal anti-inflammatory drugs (NSAIDs) after 1 week of therapy, tamponade physiology, and myocardial involvement among others.[6] In patients with pericarditis, female sex and corticosteroid use are known risk factors of recurrent pericarditis.[6,14,15] Younger age and subacute presentation are also associated with recurrence.[16] Recently, observational studies have posed and retrospectively validated risk scores predictive of recurrent pericarditis.[17,18]

Pathophysiology

The inflammatory cascade of pericarditis is stimulated by stressors such as viruses or percutaneous procedures. This leads to the release of mediators such as damage-associated molecular patterns, interleukin (IL)-1α, and pathogen-associated molecular patterns that bind with the toll-like receptors or nucleotide-binding oligomerization domainlike receptors of the inflammatory cells.[19,20] This leads to nucleotide-binding oligomerization domainlike receptor pyrin domain-containing (NLRP3) inflammasome polymerization and IL-1β production via these inflammatory cells. This process promotes the release of mediators such as cyclo-oxygenase and prostaglandins, which cause sequestration and activation of more inflammatory cells.[21] IL-1α and IL-1β bind to endothelial IL-1 receptors and activate endothelial adhesion molecules, which cause monocytes, neutrophils, and macrophages to infiltrate into the pericardium, promoting recurrent pericardial attacks. These cells release markers that recruit similar cells (causing amplification of this autoinflammatory cascade), promote fibroblast proliferation, and induce pathological neovascularization along the pericardial layers.[22-24] **Figure 1** describes this autoinflammatory cascade of events in much detail. Recently, Peet et al[25] showed that patients with idiopathic recurrent pericarditis share clinical and genetic features with IL-1–mediated autoinflammatory disorders, supporting the role of autoinflammatory etiology in idiopathic recurrent pericarditis. This is important from the treatment point of view, as it advocates for the use of IL-1 blockers as targeted therapies for patients. On the contrary, an autoimmune hypothesis based on molecular mimicry and production of autoantibodies may be responsible for the noninflammatory phenotype of recurrent pericarditis, which can be seen in patients with concurrent autoimmune systemic disease.[26-28]

Clinical Presentation and Diagnosis

Patients with pericarditis present with diffuse sharp chest pain, rapid in onset, improving with sitting up and leaning forward, and worsening with lying down or deep breathing (pleuritic).[29] Patients may also have low-grade intermittent fevers in the active phase of the disease. Per the 2015 ESC guidelines, diagnosis of acute pericarditis can be made with at least 2 of 4 criteria: (1) pericardial chest pain, (2) pericardial friction rub, (3) new diffuse ST-segment elevation or PR-segment depression on electrocardiogram, and (4) new or worsening pericardial effusion.[6] Recurrent pericarditis is diagnosed when one meets all 3 criteria: (1) documented first episode of acute pericarditis, (2) symptom-free interval of at least 4 weeks, and (3) subsequent recurrence based on criteria for acute pericarditis.[6] Despite pericardial chest pain, patients with a history of recurrent pericarditis may not meet other clinical criteria, especially if they are taking multiple anti-inflammatory medications.[30] Findings like elevation of inflammatory markers such as erythrocyte sedimentation rate and CRP and imaging assessments with computed tomography and cardiac magnetic resonance (CMR) can support the diagnosis in doubtful cases.[6]

Role of Inflammatory Markers

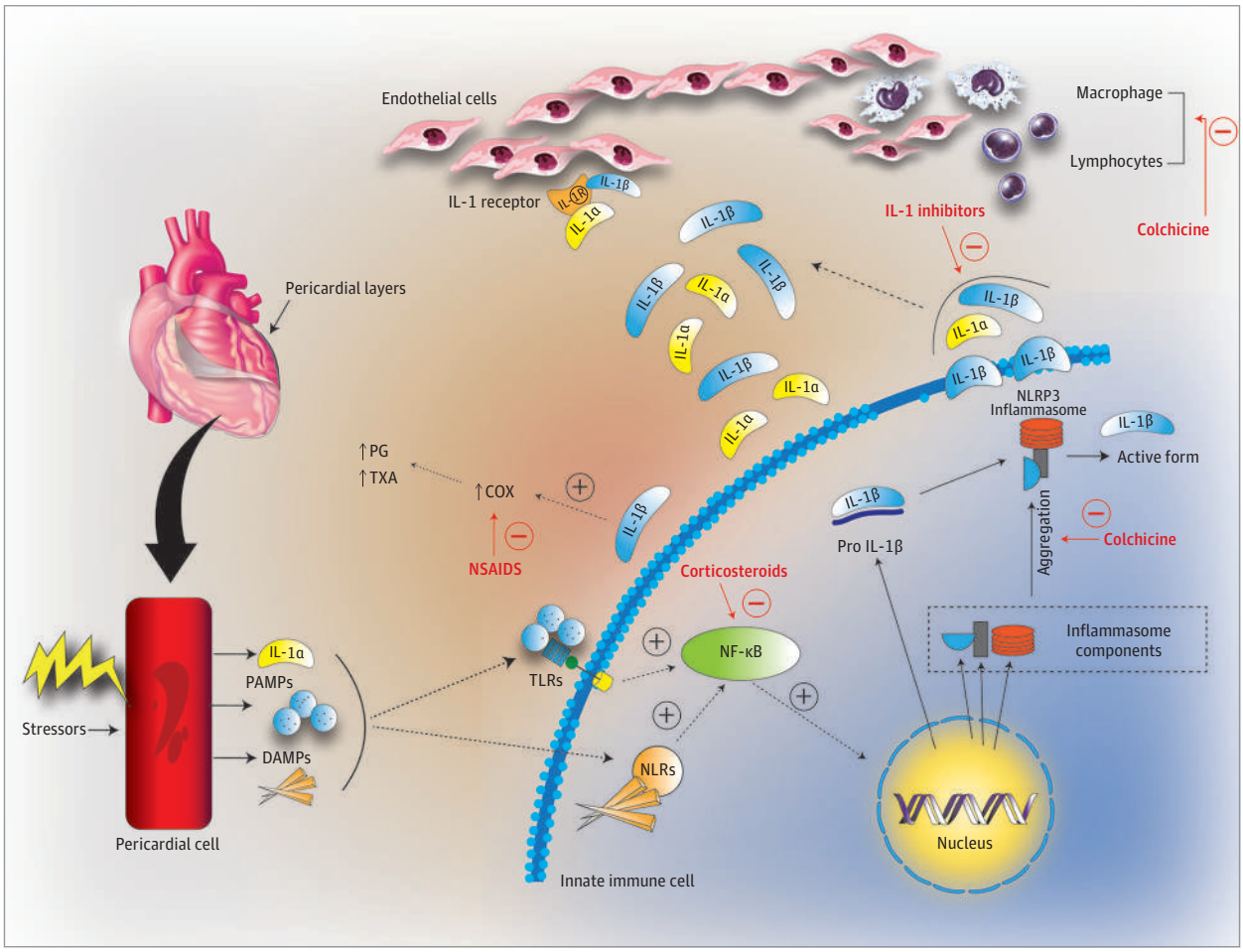
Currently, no disease-specific inflammatory marker is available for pericarditis. Current guidelines recommend using CRP and erythrocyte sedimentation rate for supporting the diagnosis of acute pericarditis/recurrence in doubtful cases, guiding treatment length, disease monitoring, and assessing the response to therapy.[6] CRP values are elevated in 96% of patients with acute pericarditis when measured at least 12 hours after symptoms.[31] High-sensitivity CRP (hs-CRP) can be used to detect lower concentrations of CRP.[32,33] On initial presentation, hs-CRP is elevated in about 80% of cases of acute pericarditis and normalizes in 60% of patients in about 1 week of therapy. Elevated hs-CRP levels at week 1 despite therapy is associated with recurrence.[34] Neutrophil-to-lymphocyte ratio and hs-CRP are independently associated with composite end point of tamponade and recurrence.[35] Patients with recurrent pericarditis with higher hs-CRP (>1 mg/dL) are less likely and require more time to achieve clinical improvement and remission than those with lower hs-CRP.[36]

Role of Imaging

For acute pericarditis, echocardiography is indicated for baseline assessment and exclusion of associated sequela such as pericardial effusion, tamponade physiology, and left ventricular dysfunction associated with myocardial involvement (**Video 1**).[6,37,38] Multiple guidelines recommend echocardiography as the first imaging test for all pericardial diseases.[6,37,38] The guidelines also recommend other imaging modalities like cardiac computed tomography or CMR to be used only for unclear cases of pericarditis when the diagnostic criteria are not met but there is high clinical suspicion. However, all the society guidelines are more than 7 years old and CMR sequencing has evolved to diagnose and stage pericardial inflammation, giving rise to pericardial characterization, which forms the backbone for individualized therapies for patients with pericardial diseases.[24,39] For patients with recurrent and constrictive pericarditis, CMR is often used to assess pericardial anatomy, cardiac hemodynamics, characterization and quantification of pericardial effusion, and disease staging, which helps with the diagnosis, monitoring, and management of the disease (**Video 2** and **Video 3**). The eTable in the Supplement summarizes different imaging modalities used for pericarditis.

CMR allows for anatomical and functional/physiological assessment of the heart. Pericardial characterization refers to detailing the anatomy and histopathology by using various sequences to identify the presence and stage of pericardial inflammation (**Table 1**).[40] This is mainly assessed using the late gadolinium enhancement (LGE) sequence and the edema-weighted T2-weighted short-tau inversion recovery sequence.[41] The pericardial LGE has very high

Figure 1. Autoinflammatory Pathway of Recurrent Pericarditis



A stressor injures the pericardium, which causes the release of interleukin (IL)-1α, pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs). These stimulate the toll-like receptors (TLRs) and nucleotide-binding oligomerization domainlike receptors (NLRs) of the innate immune cell, causing the synthesis of nuclear factor κ light chain enhancer of activated B cells (NF-κB), which induces the formation of the nucleotide-binding oligomerization domainlike receptor pyrin domain-containing (NLRP3) inflammasome and pro-IL-1β. The NLRP3 inflammasome converts pro-IL-1β to active IL-1β, which stimulates the release of prostaglandins and thromboxanes. IL-1β and IL-1α act on the IL-1 receptor (IL-1R) on capillary endothelial cells, causing migration of immune cells in the pericardium initiating/amplifying the immune response. COX indicates cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug; PG, prostaglandin; TXA, thromboxane.

sensitivity and specificity for pericardial inflammation.[42] It provides incremental information and better confirms the diagnosis of recurrence in patients with recurrent pericarditis compared with the conventional clinical criteria, suggesting the addition of LGE to conventional clinical criteria to increase its diagnostic accuracy.[30] This is further supported by a recent multicenter cohort study of 128 patients with recurrent pericarditis, showing that the presence of both LGE and pericardial edema on T2-weighted short-tau inversion recovery imaging, had a sensitivity of 73% and a specificity of 99%, which is far superior to the clinical criteria alone.[43] Importantly, CMR can also help prognosticate as shown by Kumar et al,[44] who demonstrated that lower quantitative pericardial LGE is independently associated with clinical remission, and a higher quantitative pericardial LGE is associated with shorter time to subsequent recurrence as well as a higher recurrence rate at 6 months. Such quantification remains a research tool. Clinically, a semiquantitative method (mild, moderate, and severe) for grading pericardial inflammation severity may be used based on the extent of circumferential enhancement and thickness of enhancement.[45] CMR along with the inflammatory markers can identify the patients at higher risk of complications (recurrence/constriction/tamponade) and is a helpful tool for determining treatment duration in affected patients.[43,46,47] The traditional practice is to wean therapy with resolution of inflammatory markers and symptoms; however, emerging data would suggest prolonging the taper in the presence of significant pericardial LGE as it is the last imaging biomarker of pericarditis to resolve. This forms the basis of the CMR-guided therapeutic approach for the treatment of recurrent pericarditis.[44] Use of such CMR-guided medical therapy in a retrospective analysis of 507 patients with recurrent pericarditis resulted in decreased rates of recurrence, exposure to steroids, and pericardiocentesis.[48] However, such an approach would require multiple contrast-enhanced CMR, which comes with a higher cost and may lead to gadolinium deposition, the significance of which remains unclear.[49] Epicardial fat can sometimes

Table 1. The Spectrum of Pericarditis[a]

Diagnosis	Imaging feature		Treatment
	Echocardiography	CMR[b]	
Without constrictive physiology			
Acute pericarditis	• Most common: normal • May show thickened pericardium • May show pericardial effusion	T2+ edema; LGE+ inflammation	Start anti-inflammatory therapy
Recurrent pericarditis (relapse)		T2+/−; LGE+ inflammation	Start/escalate anti-inflammatory therapy
Chronic pericarditis (>3 mo)		T2− no edema; LGE+ inflammation	Start/escalate anti-inflammatory therapy
Healed pericarditis (remission)		T2− no edema; LGE−/minimal resolved inflammation	De-escalate/taper anti-inflammatory therapy
With constrictive physiology			
Transient or effusive constrictive pericarditis	• Ventricular interdependence • Annulus reversus • Annulus paradoxus • Plethoric IVC • Prominent diastolic expiratory flow reversal in hepatic veins	T2+/−; LGE+ inflammation	Start/escalate anti-inflammatory therapy
Constrictive pericarditis		T2− no edema; LGE+/−	If LGE+, provide anti-inflammatory therapy; if LGE−, provide diuresis or pericardiectomy
Calcific constrictive pericarditis	• Strain reversus • Pericardial effusion in case of effusive constrictive pericarditis	T2− no edema; LGE− no inflammation	Diuresis or pericardiectomy
Burned-out pericarditis		Thickened pericardium (due to fibrosis and/or calcification)	

Abbreviations: CMR, cardiac magnetic resonance; IVC, inferior vena cava; LGE, late gadolinium enhancement.

[a] Pericardial characterization exhibited by CMR informs where the patient stands on the continuum of pericarditis. Pericardial characterization is assessed using the LGE sequence and the T2 sequence.

[b] LGE+ with T2+ signifies acute inflammation, LGE+ with T2− suggests subacute/chronic inflammation, and LGE− T2− represents the absence of active inflammation.

be confused with pericardial LGE enhancement; therefore, fat suppression LGE sequence may be used to improve the specificity of identifying pericardial enhancement.

Inflammation of the pericardium may result in decreased pericardial compliance leading to constrictive physiology. This is unlike the traditional fibrotic/calcific constrictive pericarditis and resolves either spontaneously or with anti-inflammatory medications and is often labeled as transient constrictive pericarditis.[50,51] In some cases of pericarditis associated with large pericardial effusion, constrictive physiology of the inflamed noncompliant pericardium is uncovered after the drainage of effusion; these cases are referred to as effusive constrictive pericarditis.[52,53] Because of the presence of the treatable inflammatory component, transient and effusive pericarditis are associated with a favorable prognosis. In a series of 33 patients with effusive constrictive pericarditis, only 2 required a pericardiectomy, while 81% of patients had total resolution of their symptoms and constrictive physiology.[54] Thus, identifying pericardial inflammation in patients with constrictive physiology is essential to redefine the disease course and spare them from long-term complications and pericardiectomy. The LGE and T2-weighted short-tau inversion recovery imaging of CMR can provide insight into the severity and time of onset of pericardial inflammation. Cremer et al[55] demonstrated how quantification of pericardial LGE, when added to clinical factors and erythrocyte sedimentation rate, can predict clinical improvement in patients with constrictive pericarditis treated with anti-inflammatory therapy. One should note that in patients with healed pericarditis, minimal pericardial LGE might persist likely secondary to permanent neovascularization. Multiple recurrences of pericarditis can eventually lead to burned-out fibrosed pericardium refractory to anti-inflammatory medications and can lead to constriction.

Cardiac computed tomography with its high spatial resolution is the most sensitive modality to detect pericardial calcification.[56] Cardiac computed tomography can also detect pericardial thickening, which if accompanied by iodinated contrast enhancement of pericardium, is suggestive of ongoing inflammation.[56]

Treatment

The goal of treatment for pericarditis is to decrease the pericardial inflammation. This is achieved with anti-inflammatory medications, which traditionally include NSAIDs, colchicine, steroids, and other steroid-sparing agents such as azathioprine, intravenous immunoglobulin, and methotrexate. More recently, IL-1 blockers such as anakinra and rilonacept have demonstrated marked efficacy. **Table 2** summarizes the landmark trials of medications used for pericarditis.[57-64] These treatment options are deployed and discontinued in a stepwise measure under close monitoring to prevent relapse. The decision to treat (start/escalate), taper, or stop therapy depends on the extent of inflammation. This extent has traditionally been informed by the symptomatology and the biochemical markers of the patient. However, for patients taking anti-inflammatory medications, these markers can have limited sensitivity and specificity.[44] In this setting, CMR provides more evidence for determining the extent of pericardial inflammation to improve management decisions.

Established Medical Therapies

NSAIDs represent the mainstay of treatment of acute and recurrent pericarditis.[29,65] Aspirin (2-4 g/d) is preferred for patients with concomitant cardiovascular disease.[66] The recommended initial

Table 2. Key Randomized Clinical Trials of Therapies for Pericarditis

Source	Trial name	No. of patients	Study population	Comparison	Primary end point	Results
Imazio et al,[15] 2005	CORE trial	84	First episode of recurrent pericarditis	Colchicine + aspirin vs aspirin alone	Recurrence rate	Colchicine decreased the recurrence rate. Recurrence rate was 24% with colchicine + aspirin and 50.6% with aspirin only (NNT, 4 [95% CI, 2.5-7.1]; *P* = .02)
Imazio et al,[57] 2005	COPE trial	120	Acute pericarditis	Colchicine + aspirin vs aspirin alone	Recurrence rate	Colchicine + aspirin led to less recurrence than aspirin alone. Recurrence rates at 18 mo were 10.7% in the colchicine + aspirin group and 32.3% in the aspirin-only group (NNT, 5; *P* = .004)
Imazio et al,[58] 2010	COPPS trial	360	Undergoing cardiac surgery	Colchicine vs placebo	Incidence of postpericardiotomy syndrome at 12 mo	Colchicine decreases the incidence of postpericardiotomy syndrome. Incidence of postpericardiotomy in the colchicine vs placebo group was 8.9% vs 21.1%, respectively (RRR, 57.9% [95% CI, 27.3-75.6]; NNT, 8; *P* = .002)
Imazio et al,[59] 2011	CORP trial	120	First recurrence of pericarditis	Colchicine + aspirin/ibuprofen vs placebo + aspirin/ibuprofen	Recurrence rate at 18 mo	Colchicine is effective for secondary prevention of recurrent pericarditis. Recurrence rate was 24% in the colchicine group and 55% in the placebo group (RRR, 0.56 [95% CI, 0.27-0.73]; NNT, 3; *P* < .001)
Imazio et al,[60] 2013	ICAP trial	240	Acute pericarditis	Colchicine + aspirin/ibuprofen vs placebo + aspirin/ibuprofen	Incessant or recurrent pericarditis	Colchicine, when added to aspirin/ibuprofen, reduced the rate of incessant or recurrent pericarditis. Primary outcome occurred in 16.7% of patients in the colchicine group and 37.5% of patients in the placebo group (RRR, 0.56 [95% CI, 0.30-0.72]; NNT, 4; *P* < .001)
Imazio et al,[61] 2014	COPPS-2 trial	360	Undergoing cardiac surgery	Colchicine vs placebo	Occurrence of postpericardiotomy within 3 mo	Perioperative use of colchicine reduced the incidence of postpericardiotomy syndrome. The primary end point was seen in 19.4% of patients in the colchicine arm and in 29.4% of patients in the placebo arm (absolute difference, 10.0% [95% CI, 1.1%-18.7%]; NNT, 10)
Imazio et al,[62] 2014	CORP-2 trial	240	Multiple recurrences of pericarditis (≥2)	Colchicine + aspirin/NSAIDs vs placebo + aspirin/NSAIDs	Recurrent pericarditis	Colchicine + aspirin/NSAIDs significantly reduce recurrences of pericarditis in patients with multiple recurrences. Recurrence rate was 21.6% in the colchicine arm and 42.5% of patients in the placebo arm (relative risk, 0.49 [95% CI, 0.24-0.65]; *P* < .001; NNT, 5)
Brucato et al,[63] 2016	AIRTRIP trial	21	Recurrent pericarditis (with ≥3 recurrences), elevation of CRP, colchicine resistance, and corticosteroid dependence	Anakinra vs placebo	Recurrent pericarditis and time to recurrence postrandomization	Use of anakinra compared with placebo reduced the risk of recurrence of pericarditis for patients with recurrent pericarditis with colchicine resistance and corticosteroid dependence. Recurrent pericarditis occurred in 9 of 10 patients in placebo group and 2 of 11 in anakinra group. Median (IQR) time to recurrence was 72 (64-150) days after randomization in placebo group and was not reached in anakinra arm (*P* < .001)
Klein et al,[64] 2021	RHAPSODY trial	61	Recurrent pericarditis patients with at least a second recurrence, despite NSAIDs, colchicine, or oral glucocorticoids in any combination. Pain numeric rating scale ≥4, CRP≥1 mg/dL	Rilonacept vs placebo	Time to first pericarditis recurrence	For patients with recurrent pericarditis, rilonacept led to rapid resolution of the recurrence episodes and decreased the risk of further recurrences. Too few (2 of 30) recurrences occurred in the rilonacept arm for the median time for recurrence to be calculated vs median time to recurrence (23 of 31) in placebo group was 8.6 wk (HR, 0.04 [95% CI, 0.01-0.18]; *P* < .001)

Abbreviations: CRP, C-reactive protein; HR, hazard ratio; NNT, number needed to treat; NSAIDs, nonsteroidal anti-inflammatory drugs; RRR, relative risk reduction.

dose of oral ibuprofen is 600 to 800 mg every 8 hours and oral indomethacin is 50 mg every 8 hours. Adverse events of NSAIDs include gastric ulceration, arterial hypertension, and kidney failure.[29] To mitigate the adverse events associated with NSAIDs, patients should be prescribed proton-pump inhibitors for gastroprotection and have periodic laboratory work to monitor nephrotoxicity.

Colchicine, along with NSAIDs, is the first-line therapy for the management of acute and recurrent pericarditis.[6,62] The use of colchicine in the CORE (Colchicine for Recurrent Pericarditis) trial[15] and the CORP (Colchicine for Recurrent Pericarditis) trial[59] resulted in a decreased rate of recurrences, improved rate of remission, and hastened resolution of symptoms in patients with recurrent pericarditis. The COPE study[57] and the ICAP (Investigation on Colchicine for Acute Pericarditis) study[60] were the first randomized clinical trials, to our knowledge, that showed the efficacy of colchicine for acute pericarditis during the initial attack and a decrease in the rate of incessant and recurrent pericarditis. In a meta-analysis of 1981 patients with pericarditis by Lutschinger et al,[67] colchicine reduced recurrence rate and incidence of postpericardiectomy syndrome. The recommended dose is 0.6 mg twice daily; however, once daily is recommended for patients with weight less than 70 kg.[6] Dose reduction should be considered for patients who develop gastrointestinal symptoms (anorexia, diarrhea, nausea, vomiting) or weakness related to the drug therapy.[29] Other adverse events include alopecia and polyneuropathy.

Corticosteroids are added for patients with incomplete or no resolution of symptoms with NSAIDs and colchicine.[6] Corticosteroids are also indicated in cases of intolerance or contraindication to NSAIDs/colchicine. Although corticosteroids provide rapid relief of symptoms, their use is associated with increased risk of recurrence and chronicity, which can further lead to steroid-related adverse events.[7,68] The COPE (Colchicine for Acute Pericarditis) trial[57] showed a 4.3-fold increased risk of recurrence with the use of corticosteroids.[60] When used, low to moderate doses of prednisone (0.2-0.5 mg/kg/d) is recommended as it has better potency and lower risk of adverse events compared with higher doses.[68,69] Corticosteroid tapering should only be initiated after complete resolution of symptoms and normal CRP levels.[68] Slow tapering is recommended (1-2.5 mg every 2-6 weeks) when dosing reaches a certain threshold (10-15mg/d), as rapid tapering is associated with high rates of recurrence.[6]

Immunosuppressants such as azathioprine are mainly used as steroid-sparing agents.[70] In a single-center study of 46 patients, azathioprine was associated with remission in more than 50% of patients with idiopathic recurrent pericarditis following steroid discontinuation.[71] The most common adverse event is myelosuppression, which is generally dose-dependent and resolves after 7 to 10 days.[71] Other immunosuppressive drugs such as methotrexate, hydroxychloroquine, and mycophenolate mofetil have also been used but have limited data.[72,73] Based on limited experience, the 2015 ESC guidelines gave a class IIb recommendation for the use of azathioprine and intravenous immunoglobulins[74,75] as third-line agents for recurrent pericarditis.[6] The same level of recommendation was provided for the use of anakinra[76,77] as a third-line treatment in patients with colchicine-resistant corticosteroid-dependent recurrent pericarditis.[6] For such patients, before adding agents such as immunoglobulins, azathioprine, or IL-1 inhibitors, one should consider consultation with immunologists/rheumatologists.[6] In addition, rheumatology consultation may be important to rule out an autoimmune etiology vs idiopathic/viral etiology.

Emerging Medical Therapies

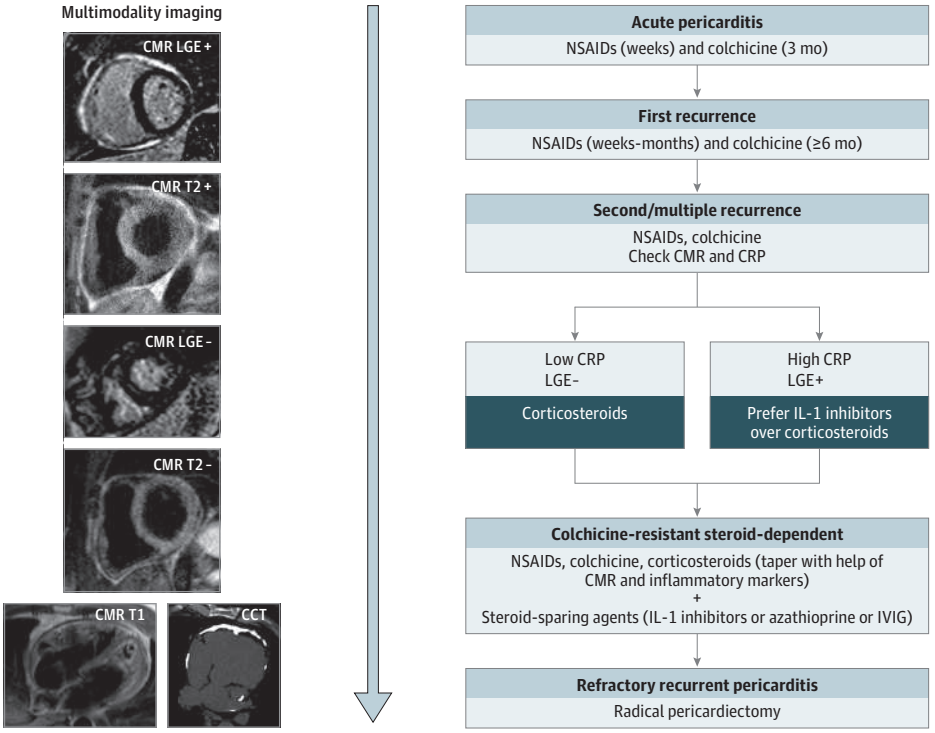
IL-1 blockers are recommended for infection-negative, corticosteroid-dependent patients with recurrent pericarditis who are not responsive to colchicine.[6] Since the 2015 ESC guidelines, there has been significant growth in evidence for IL-1 inhibitors. The 3 available agents for pericarditis are rilonacept, canakinumab, and anakinra. Rilonacept is a dimeric fusion protein that traps IL-1α and IL-1β, canakinumab is an IgG1 human monoclonal antibody targeted at IL-1β, and anakinra is a recombinant human IL-1 receptor antagonist.[78]

Rilonacept traps IL-1α and IL-1β and prevents their fusion with the IL-1 receptor, hence breaking the auto-catalytic cycle of pericardial inflammatory cascade.[79] Its efficacy was first demonstrated in a pilot study of 25 patients with recurrent pericarditis, in which rilonacept showed a rapid and sustained improvement in pain and inflammation along with tapering and discontinuation of corticosteroids.[80] The drug was then tested in the RHAPSODY (Rilonacept Inhibition of Interleukin-1 Alpha and Beta for Recurrent Pericarditis: a Pivotal Symptomatology and Outcomes Study) trial,[64] which randomized 61 colchicine-resistant glucocorticoid-dependent patients with recurrent pericarditis into the rilonacept and placebo arm. Patients were treated with 12 weeks of rilonacept, and their background anti-inflammatory medications were tapered and discontinued. After achieving remission, patients were randomly assigned to receive either rilonacept or a placebo. Recurrence occurred in 23 patients (74%) treated with placebo compared with 2 patients (7%) treated with rilonacept with a median time to recurrence of 8.6 weeks in the placebo group. Based on these results, rilonacept became the first drug to be approved by the US Food and Drug Administration to treat recurrent pericarditis and reduce the risk of recurrence.[64] The initial adult dosage of the subcutaneous injection is 320 mg, followed by weekly doses of 160 mg. Given the gradual washout period of rilonacept of 5 to 8 weeks, and median rilonacept treatment of 9 months (maximum, 15 months), consideration may be given to stopping it without tapering. However, further studies are needed to address this idea in the long-term extension of the RHAPSODY trial. At this time, the exact duration of rilonacept therapy for recurrent pericarditis is unclear. Adverse effects of rilonacept include mild-moderate injection site reactions and upper respiratory tract infections.

Canakinumab is not commonly used to treat pericarditis because of its high cost and paucity of data. Its efficacy was suggested by a case series of 3 patients with rheumatic disease–associated colchicine-resistant, corticosteroid-dependent recurrent pericarditis who previously failed response to biologic agents including anakinra, in whom a response was achieved in 2 patients.[81] Subsequent case reports[82,83] continued providing mixed results, with the conclusion that canakinumab fails to achieve stable remission of pericarditis. This may be attributed to the selective blockade of the IL-1β.[78]

After the 2015 ESC guidelines, AIRTRIP (Anakinra—Treatment of Recurrent Idiopathic Pericarditis) trial[63] and the IRAP (International Registry of Anakinra for Pericarditis)[84] registries are 2 prominent studies that have emerged supporting the role of anakinra for recurrent pericarditis. AIRTRIP was a double-blinded random-

Figure 2. Proposed Algorithm for Recurrent Pericarditis



In patients with multiple recurrences of pericarditis (>2), we recommend checking cardiac magnetic resonance (CMR) and C-reactive protein (CRP) to identify the patients with an inflammatory phenotype (increased pericardial inflammation as late gadolinium enhancement [LGE]+ and CRP level of >1 mg/dL). For such patients, an interleukin (IL)-1 inhibitor might be preferred over corticosteroids. This recommendation is primarily based on our practice and proven success of IL-1 inhibitors for corticosteroid dependent inflammatory recurrent pericarditis. The left panel shows how with disease progression, with multiple recurrences, the ongoing inflammation in the pericardium decreases, eventually leading to burned-out fibrosed pericarditis that is refractory to medical management. CCT indicates cardiac computed tomography; IVIG, intravenous immunoglobulin; NSAID, nonsteroidal anti-inflammatory drug.

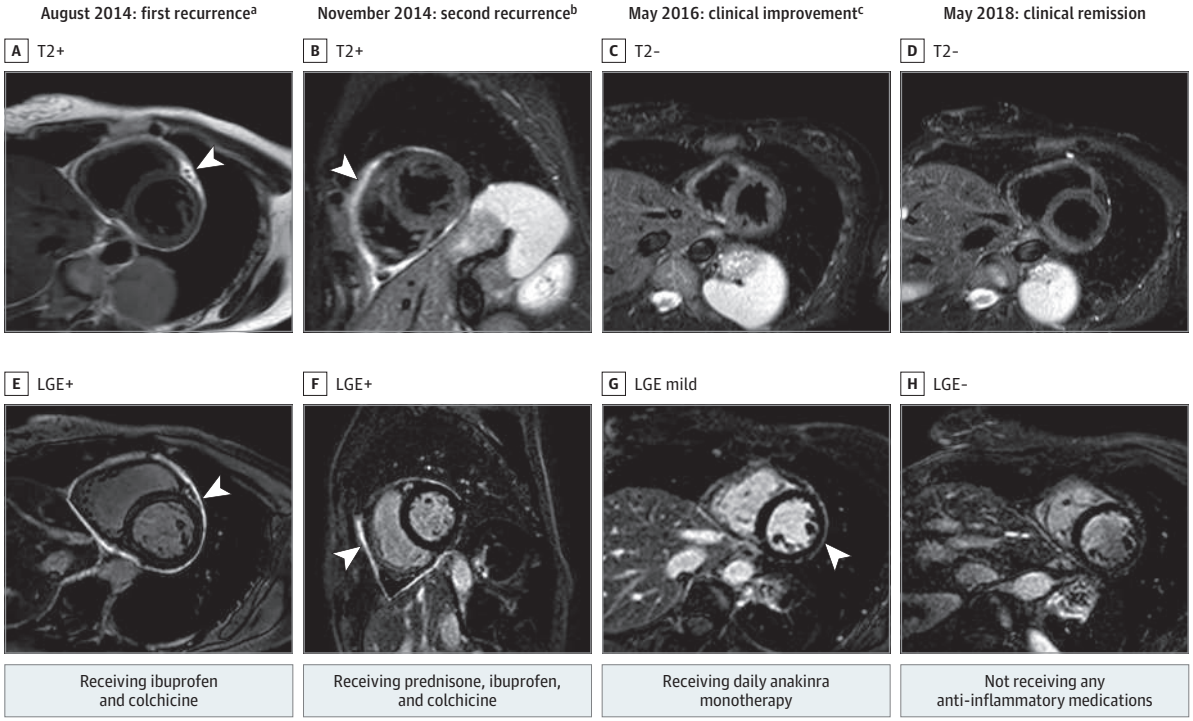
ized trial of 21 patients that showed anakinra to be associated with a marked reduction in recurrence for colchicine-resistant, glucocorticoid-dependent patients with recurrent pericarditis over a median of 14 months.[63] The IRAP registry included 224 patients who showed a reduction in pericarditis recurrence (from 2.3 to 0.4 recurrences per patient per year) and corticosteroid usage (from 80% to 27%) with 6 months of treatment with anakinra.[84] However, irrespective of the tapering protocol, rate of recurrence was 11% to 50%. In a recent meta-analysis by Imazio et al[85] involving 397 patients, anakinra was associated with more than 90% reduction in pericarditis recurrences compared with placebo and/or standard therapy. The initial dosage of the subcutaneous injection is 1 to 2 mg/kg (up to 100 mg) daily. Once the symptom control is achieved, gradual tapering is suggested with a reduction of 100 mg/week every 1 to 2 months with monitoring of symptoms and inflammatory laboratory/imaging biomarkers.[86] The high cost of IL-1 inhibitors remains a major drawback, limiting widespread use of these agents.

The efficacy of IL-1 blockers in recurrent pericarditis has resulted in a paradigm shift in the management of these patients.[85] Accordingly, we anticipate and recommend an upgrade in the guidelines with regards to the use of anti-IL-1 agents for colchicine-resistant, steroid-dependent recurrent pericarditis.[78,87,88] In the absence of data and given the difficulty to wean corticosteroids in patients of recurrent pericarditis, future studies should explore the possibility of earlier use of IL-1 inhibitors in place of corticosteroids, which IL-1 inhibitor is more efficacious, and ideal tapering protocols. In the future, there could be customized targeted therapy involving IL-blockers based on genetic analysis.[89] Given the proven efficacy of IL-1 inhibitors for inflammatory corticosteroid-dependent recurrent pericarditis and our clinical experience of managing such patients, we recommend a more up-front use of IL-inhibitors and propose a state-of-the-art algorithm (**Figure 2**) that integrates advanced cardiac imaging and biologics with the current management of pericarditis.

Surgery

Indications of pericardiectomy include refractory recurrent pericarditis, constrictive pericarditis, select cases of chylopericardium that fail conservative therapy, and recurrent pericardial effusions, especially when loculated or when biopsy material is required.[6] Pericardiectomy can be considered for patients with recurrent pericarditis with debilitating symptoms after a thorough trial of unsuccessful medical therapy, referred to as refractory recurrent pericarditis. These patients should be referred to specialty centers with surgeons having specific expertise in pericardiectomy.[6,90] Typically, chest pain improves dramatically, but it may persist after the surgery because of incomplete pericardiectomy or epicarditis (inflammation of the epicardial fat). For patients with constrictive pericarditis, the absence of significant pericardial LGE on CMR and/or presence of pericardial calcification on cardiac computed tomography suggests irreversibility, and pericardiectomy is indicated. While anterior phrenic-to-phrenic pericardiectomy has been widely accepted as adequate, residual posterior and diaphragmatic pericardium may lead to late recurrent constriction or contribute to inadequate symptom control in refractory recurrent pericarditis. Thus, radical pericardiectomy is preferred.[91-93] While pericardiectomy has been considered a high-risk operation with operative mortality of 6% to 10%,[94-96] recent reports from specialty centers suggest operative risk is largely dependent on etiology and comorbidities, with operative mortality for idiopathic cases less than 1.5%.[90,97,98]

Figure 3. Clinical Journey of Patient Diagnosed With Recurrent Pericarditis



The patient was diagnosed with acute pericarditis in June 2014 and started taking ibuprofen and colchicine. When she had a recurrence of chest pain in August 2014, cardiac magnetic resonance imaging (CMR) was performed, which showed circumferential increased pericardial signal intensity on T2 (A) as well as moderate pericardial late gadolinium enhancement (LGE) (E). The patient was diagnosed with recurrent pericarditis, and prednisone was added to her regimen. While tapering prednisone, she had another recurrence of chest pain in November 2014. CMR was performed, which showed persistent circumferential pericardial signal intensity on T2 (B) and persistent pericardial LGE (F), consistent with recurrence of inflammation. Given another recurrence of pericarditis, her prednisone dose was increased and azathioprine was added to her regimen. Despite taking prednisone, azathioprine, ibuprofen, and colchicine, her chest pain was not adequately controlled and she was switched from azathioprine to anakinra, which caused rapid relief of her symptoms. Eventually, she started tapering her background medications while taking anakinra. She finished all her medications while taking anakinra. On a follow-up visit in May 2016, while she was taking anakinra injections daily, a CMR was performed which showed no pericardial enhancement on T2 (C) and minimal LGE (G). Eventually, she tapered her anakinra and followed up in May 2018. While she was not taking all anti-inflammatory medications, CMR showed no T2 enhancement (D) and no pericardial LGE (H) consistent with remission.

[a] Prednisone treatment added.

[b] Azathioprine treatment added and prednisone dose increased.

[c] Anakinra treatment tapering started.

Conclusions

The clinical journey of initially described patient is illustrated in Figure 3. Recurrent pericarditis is a chronic debilitating condition that complicates up to one-third of acute pericarditis cases. For the diagnosis of recurrence, one had to traditionally rely on symptomatology and inflammatory markers, which lack the desired accuracy for patients taking anti-inflammatory medications. CMR has emerged as a comprehensive tool providing insight into the histopathology, progression, and prognosis of pericarditis by providing pericardial characterization. Data provided by CMR can help inform the decision whether to continue, taper, or intensify the anti-inflammatory regimen, allowing tailoring of therapy for recurrent pericarditis. With limited therapeutic options and the adverse event profile of various anti-inflammatory agents, the management of recurrent pericarditis is far more challenging than acute pericarditis. The addition of IL-1 blockers in the current armamentarium is a leap forward in the treatment of colchicine-resistant, corticosteroid-dependent recurrent pericarditis.

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Acquisition, analysis, or interpretation of data: Kumar, Reyaldeen, Imazio, Kwon, Klein.
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