REVIEW ARTICLE

Noninfectious pericarditis: management challenges for cardiologists

Massimo Imazio

University Cardiology, AOU Città della Salute e della Scienza di Torino, Torino, Italy

KEY WORDS
anakinra, colchicine, corticosteroids, pericarditis, recurrence

ABSTRACT
The aim of this review is to deal with management challenges related to diagnosis and therapy of noninfectious pericarditis. In the European countries in which a low prevalence of tuberculosis is noted, determining the etiology of pericarditis is essentially aimed at the exclusion of the most common causes, which may require a specific therapy and are associated with an increased risk of complications: systemic autoimmune or autoinflammatory diseases, postcardiac injury syndrome (5%–20%), neoplastic pericardial involvement (5%–10%), tuberculosis (about 5%), and rarely purulent pericarditis in less than 5% of cases. In developing countries that report a high prevalence of tuberculosis, this condition is the most common cause of pericardial diseases. The diagnosis is based on clinical criteria (pericarditis-related chest pain and pericardial rubs) complemented by laboratory (elevated levels of C-reactive protein) and imaging findings (electrocardiography, echocardiography, and other imaging modalities to provide evidence of pericardial inflammation in doubtful cases). Poor prognostic predictors (high fever >38 °C, subacute course, large pericardial effusion, cardiac tamponade, and lack of response to empiric anti-inflammatory therapies) identify high-risk patients who should be admitted to the hospital in order to determine disease etiology and receive appropriate treatment. The mainstay of medical therapy of noninfectious pericarditis is based on nonsteroidal anti-inflammatory drugs and colchicine, with possible adjunct of corticosteroids at low-to-moderate doses in unresponsive patients. Additional therapies, particularly with anakinra, have been implemented for those who develop corticosteroid dependence and are colchicine-resistant. Disease recurrence is the most common and troublesome complication of pericarditis, whereas the risk of developing constrictive pericarditis is related to the etiology and not to the number of recurrences.

Introduction Acute and recurrent pericarditis is a relatively common inflammatory disease of the pericardium, which can occur as an isolated condition or be associated with a systemic disease (eg, inflammatory systemic diseases, renal failure).[1-4] The etiology of pericarditis may be either infectious or noninfectious (TABLE 1).[3,5] In countries where a low prevalence of tuberculosis is observed, the main causes of infectious pericarditis include cardiotropic viruses (eg, enteroviruses, herpes virus, mainly Epstein–Barr virus and cytomegalovirus, and parvovirus B19).[3,6] Frequently, the viral etiology is only presumed after excluding other more common causes, since the definitive diagnosis would require performing pericardial biopsy, which is not warranted in most cases with a self-limiting and benign course of the disease. Serology is often used in clinical practice for presumptive etiological diagnosis, but it simply confirms the presence of a recent viral infection (eg, by titers of immunoglobulin M antibodies) or previous viral infection (eg, by titers of immunoglobulin G antibodies) without providing a definitive diagnosis of pericardial infection.[3] In countries that report a high prevalence of tuberculosis, this disease is the main cause of pericarditis, often exudative with a high risk of evolution into constrictive pericarditis. Based on that, all over the world, tuberculosis is the main cause of pericardial diseases and should always be considered and ruled out particularly in immigrants or immunodepressed patients.[3,6]

Correspondence to:
Massimo Imazio, MD, FESC, University Cardiology, AOU Città della Salute e della Scienza di Torino, Corso Bramante 88, 10126 Torino, Italy, phone: +39 0116335538, Twitter: @ImazioMassimo, email: massimo_imazio@yahoo.it
Received: May 10, 2020.
Revision accepted: May 11, 2020.
Published online: May 11, 2020.
Kardiol Pol. 2020; 78 (5): 396-403
doi:10.33963/KP.15353

TABLE 1 Etiology of pericarditis

Infectious	Viral[a] (common): enteroviruses, herpes viruses (mainly Epstein–Barr virus and cytomegalovirus), adenoviruses, and parvovirus B19
	Bacterial: mainly *Mycobacterium tuberculosis*[a]; other bacterial agents are less common
	Fungal (very rare): *Histoplasma* spp (in immunocompetent patients), *Aspergillus* spp, and *Candida* spp (in immunosuppressed patients)
	Parasitic (very rare): *Echinococcus* spp and *Toxoplasma* spp
Noninfectious	Autoimmune (systemic inflammatory diseases[a]: mainly SLE, rheumatoid arthritis, Sjögren syndrome, scleroderma, vasculitis, and mainly Behçet syndrome)
	Neoplastic[a] (mainly secondary to lung cancer, breast cancer, lymphoma, leukemias, and melanoma)
	Postcardiac injury syndromes[a] (after acute myocardial infarction, PCI, pacemaker implantation, ICD implantation, ablation of arrhythmias, and cardiac or thoracic surgery)
	Autoinflammatory diseases (eg, familial Mediterranean fever[a])
	Metabolic (renal failure, hypothyroidism)
	Drug-related (rare): lupus-like syndrome (eg, due to procainamide, hydralazine, methyldopa, isoniazid, and phenytoin) Chemotherapy (eg, due to anthracyclines) Hypersensitivity with eosinophilia (eg, due to penicillins, mesalazine, clozapine, and vaccines)

a One of the main causes

Abbreviations: ICD, implantable cardioverter-defibrillator; PCI, percutaneous coronary intervention; SLE, systemic lupus erythematosus; spp, species

This review focuses on noninfectious pericarditis and discusses the management of "idiopathic pericarditis," that is, pericarditis of unknown etiology, diagnosed after proper diagnostic workup performed according to the 2015 European Society of Cardiology (ESC) guidelines.[3] The aim of this review is to deal with management challenges related to diagnosis and therapy of pericarditis, which are faced by cardiologists. To provide a comprehensive and up-to-date paper, several electronic databases (Pubmed, Cochrane Library, MEDLINE, EMBASE, Scopus, and Google Scholar) have been reviewed using the search terms "pericarditis" and "diagnosis" or "therapy," from inception through April 2020.

Challenges in determining the etiology

In the European countries reporting a low prevalence of tuberculosis, the search for etiology is essentially aimed at excluding the most common causes of pericarditis (TABLE 2),[7-11] which may require specific treatment and are associated with an increased risk of complications: systemic autoimmune or autoinflammatory conditions,[12] postcardiac injury syndrome (5%–20%),[13] neoplastic pericardial involvement (5%–10%),[7-11,14] tuberculosis (about 5%),[6,11] and rarely purulent pericarditis in less than 5% of cases.[3] Even when a systematic search for etiology is conducted, most cases remain uncomplicated and "idiopathic" or are presumed to be of viral or postviral origin.[5] In these settings, if pericarditis is self-limiting and responsive to empiric anti-inflammatory therapies, it is not recommended to perform additional diagnostic testing, since the management is the same.[3] Determining the specific viral agent would require detecting the infectious agent directly in the pericardium (pericardial biopsy) or pericardial fluid (pericardiocentesis), since viral serology can be useful

TABLE 2 Main causes of pericarditis reported in several case series of patients with acute pericarditis

Variable		Soler-Soler et al[7]	Zayas et al[8]	Reuter et al[9]	Imazio et al[10]	Gouriet et al[1]
Patients, n		231	100	233	453	933
Years		1977–1983	1991–1993	1995–2001	1996–2004	2007–2012
Site		Spain	Spain	South Africa	Italy	France
Pericarditis, n (%)	Idiopathic	199 (86)	78 (78)	32 (13.7)	377 (83.2)	516 (55)
	Autoimmune[a]	4 (1.7)	3 (3)	12 (5.2)	33 (7.3)	197 (21)
	Neoplastic	13 (5.6)	7 (7)	22 (9.4)	23 (5.1)	85 (8.9)
	Tuberculous	9 (3.9)	4 (4)	161 (69.5)	17 (3.8)	4 (<1)
	Purulent	2 (0.9)	1 (1)	5 (2.1)	3 (0.7)	29 (3)

a Including systemic autoimmune diseases, inflammatory diseases, and postcardiac injury syndromes

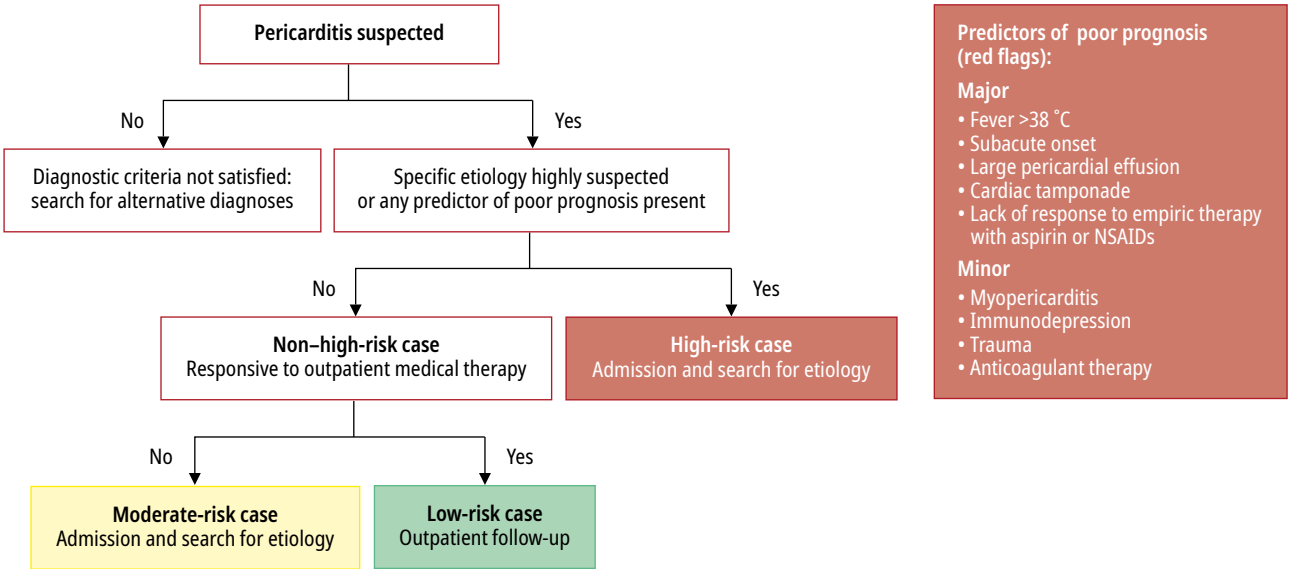


FIGURE 1 Triage of patients with pericarditis
Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs

only to diagnose recent viral infection without clear evidence of pericardial infection. Invasive testing with pericardiocentesis has generally a low diagnostic yield in the absence of cardiac tamponade or with moderate-to-large pericardial effusions suspected to be of bacterial or neoplastic etiology.[3,5,15]

Diagnostic issues In clinical practice, the diagnosis of pericarditis is based on clinical criteria that have been formulated in previous prospective studies.[7,8,10,16] These criteria have been endorsed by the 2015 ESC guidelines and include: 1) pericarditic chest pain; 2) pericardial rubs; 3) suggestive changes detected on electrocardiography (ECG; widespread PR--segment depression and ST-segment elevation as early signs); and 4) new or worsening pericardial effusion.[3] At least 2 of these 4 criteria should be present to establish a definitive clinical diagnosis of pericarditis (TABLE 3). However, in clinical practice, the relative frequency of manifestations included in these clinical criteria varies regarding presentation times and setting (acute versus recurrent pericarditis). In acute or recurrent pericarditis, pericarditic chest pain is reported in the majority of patients, and it is the usual reason for presentation, whereas other findings are more common in acute forms, and not during recurrences. For instance, pericardial rubs have been reported in one-third of cases in acute pericarditis,[7,8,10,16] but are uncommon for recurrences. The same is also true for changes seen on ECG: widespread ST-segment elevation is usually associated with some degree of myocardial involvement (>60% of cases with concomitant myocarditis) but less common in simple pericarditis, since the pericardium is electrically silent, and ECG changes reflect myocardial involvement.[17,18] The typical ECG evolution in 4 stages (FIGURE 1) is also rare in recurrences and depends on presentation time: ST-segment elevation can be seen at early stages, particularly with

TABLE 3 Diagnostic criteria for pericarditis according to the current European Society of Cardiology guidelines[3]

Setting	Diagnostic criteria
Acute	Clinical criteria (at least 2 of the following 4): 1) pericarditic chest pain; 2) pericardial rubs; 3) new widespread ST-segment elevation or PR-segment depression on ECG; and 4) pericardial effusion (new or worsening) Additional supporting findings: biomarkers (CRP levels, erythrocyte sedimentation rate, and WBC count), imaging (evidence of pericardial inflammation detected on imaging [CT, cardiac MRI])
Incessant	Pericarditis lasting for more than 4 to 6 weeks but less than 3 months without remission
Recurrent	Episode of pericarditis with a symptom-free interval of 4 to 6 weeks or longer from the previous attack
Chronic	Pericarditis lasting longer than 3 months

Abbreviations: CRP, C-reactive protein; CT, computed tomography; ECG, electrocardiography; MRI, magnetic resonance imaging; WBC, white blood cell

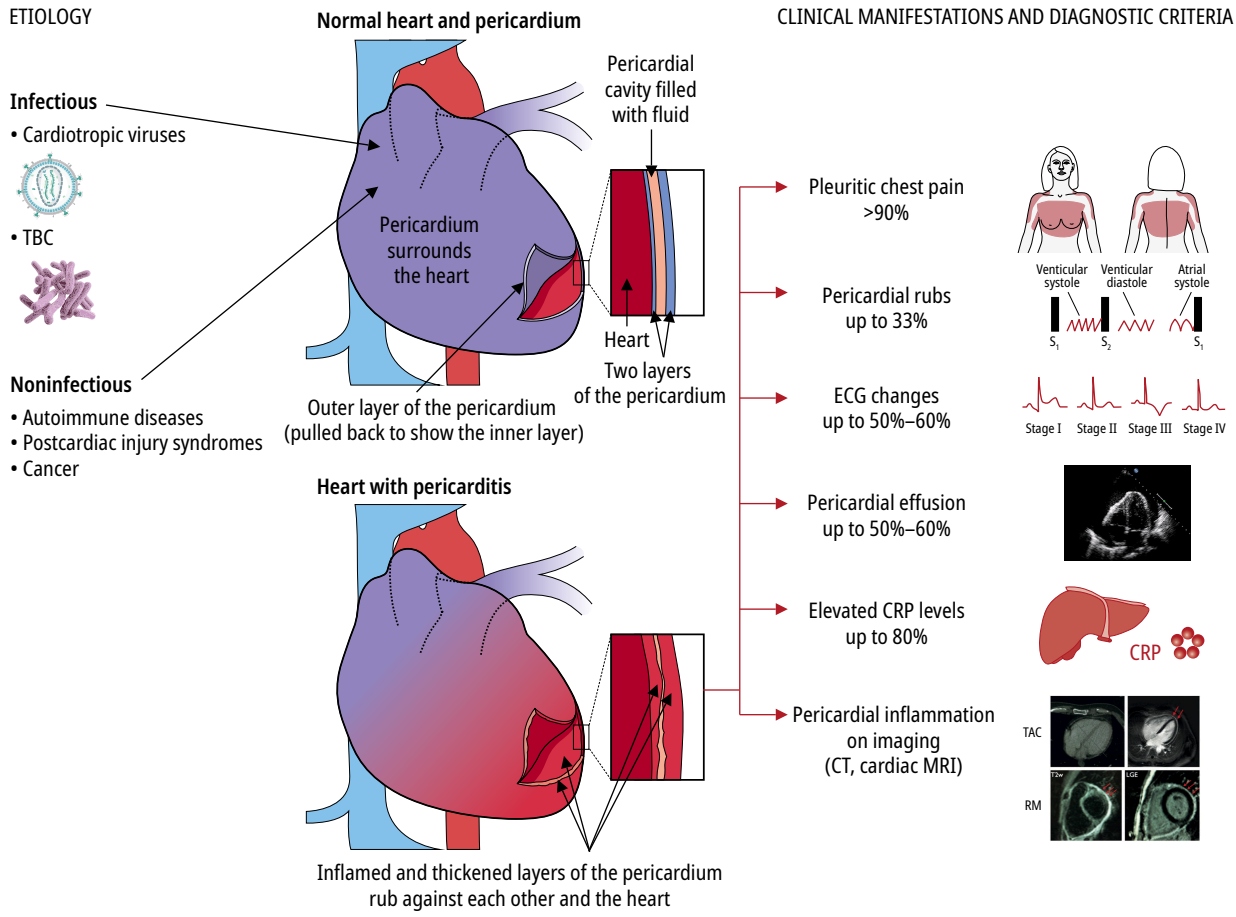
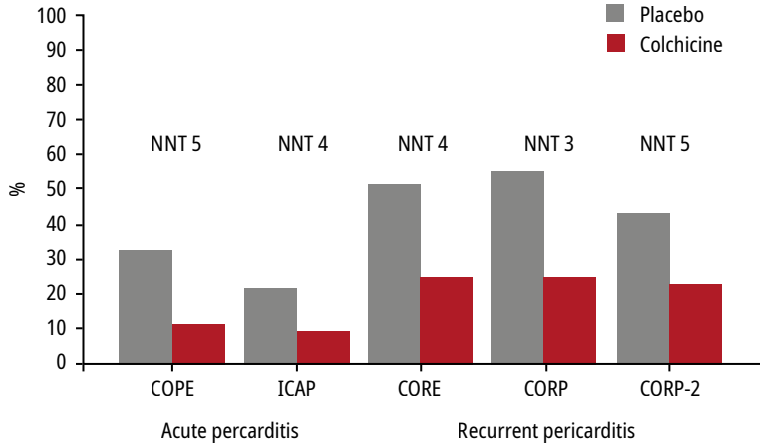


FIGURE 2 Main manifestations of pericarditis and criteria for its diagnosis
Abbreviations: TBC, tuberculosis; others, see TABLE 3

concomitant myocarditis, but it is less common in late presentations when only atypical ST-segment and T-wave changes can be documented and even normal ECG does not exclude pericarditis by itself.[3] Pericardial effusion is reported in 50%–60% of cases of acute pericarditis, but it is less common in recurrences. Moreover, pericardial effusion can be reported even in the absence of pericarditis (eg, in uremia, hypothyroidism, systemic inflammatory diseases, heart failure, pulmonary hypertension, and cancer), and, thus, it is not essential for the diagnosis of pericarditis, that is "dry pericarditis," in at least 50% of cases.[19,20] Based on that, the 2015 ESC guidelines provide additional supporting criteria for clinical diagnosis, which can be used when the standard ones are insufficient: 1) biomarkers (especially elevated levels of C-reactive protein [CRP])[3,21] and 2) evidence of pericardial inflammation on imaging (computed tomography and cardiac magnetic resonance imaging, as the inflamed pericardium is basically neovascularized and can be enhanced with contrast)[3,22] (FIGURE 2).

Triage and admission criteria Patients with pericarditis of a specific etiology (nonviral or idiopathic) are at higher risk of complications (recurrences, cardiac tamponade, and constriction). Some clinical features at presentation can be used to predict the increased risk of nonidiopathic pericarditis and complications. These features are poor prognostic predictors and include: high fever (>38 °C; hazard ratio [HR], 3.6), unusual for uncomplicated viral or idiopathic pericarditis, subacute course (without acute onset or without pericarditic chest pain; HR, 4), large pericardial effusion (>20 mm as the largest telediastolic echo-free space) or cardiac tamponade at presentation (HR, 2.1–2.5), and failure to respond to empiric anti-inflammatory therapy with aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs; HR, 2.5–5.5). Female sex is associated with an increased risk of developing complications or pericarditis of nonidiopathic etiology (HR, 1.6–1.7).[10,16] According to experts' opinion, additional features to be considered as potential risk factors include: concomitant myocarditis (these patients are admitted for differential diagnosis and monitoring of the response to medical therapies), recent chest trauma, use of oral anticoagulants, and immunosuppressive conditions.[3,23,24]

Since patients presenting with none of these features usually have a benign, often self-limiting, disease course and respond to



Adverse effects:
Diarrhea (about 8%)
Elevated levels of transaminases (4%)
Leukopenia, alopecia (<1%)

Drug–drug interactions:
Possible in elderly patients and those with renal failure
(halved doses are recommended in this population)
Consider concomitant treatment with statins and macrolides

FIGURE 3 Main clinical trials[29-33] on the use of colchicine in acute and recurrent pericarditis showed that recurrence rates were halved in patients treated with colchicine (red bars) on top of other anti-inflammatory drugs (nonsteroidal anti-inflammatory drugs or corticosteroids) compared with those not treated with colchicine or receiving placebo (gray bars) during long-term follow-up of up to 18 months
Abbreviations: COPE, COlchicine for PEricarditis; CORE, COlchicine for RECurrent pericarditis; CORP, COlchicine for Recurrent Pericarditis; CORP-2, COlchicine for Recurrent Pericarditis-2; ICAP, Investivation on Colchicine for Acute Pericarditis; LOE, level of evidence; NNT, number needed to treat

empiric anti-inflammatory therapies, there is no reason to admit all patients with pericarditis. According to available evidence and guidelines,[3] patients with pericarditis can be triaged at presentation, based on the presence or absence of poor prognostic predictors (FIGURE 1).[3,23,24] In this way, patients are classified as high-risk cases (if at least 1 poor prognostic predictor is present) and non–high-risk cases (if no poor prognostic predictor is reported). Patients at high risk are admitted to the hospital to determine the disease etiology and monitor their response to therapy.[3,5] Those without poor prognostic predictors are treated on an outpatient basis, with empiric anti-inflammatory therapy and planned follow-up after 1 to 2 weeks aimed to assess the response to therapy, carry out basic blood tests (eg, complete blood count, CRP, transaminase, creatinine, and creatine kinase levels), and perform echocardiography to detect possible pericardial effusion and additional signs of constriction. Patients responding to medical therapy are considered to be at low risk and, if asymptomatic without relapses, may not require additional testing. Patients who do not fully respond to medical therapy at 1 to 2 weeks should be reassessed for admission or additional testing in order to determine the disease etiology and introduce alternative therapies.[3,10,16]

Treatment issues Although the treatment of pericarditis also depends on the cause of the condition (eg, a systemic inflammatory disease or cancer), in clinical practice, the majority

TABLE 4 Common medical therapies for noninfectious pericarditis

Drug	Mechanism of action	Daily dose during an attack	Usual duration of treatment with an attack dose[a]	LOE[b]
Aspirin	COX inhibition	750–1000 mg 3 times a day	1–2 weeks	B
Ibuprofen	COX inhibition	600–800 mg 3 times a day	1–2 weeks	B
Indomethacin	COX inhibition	25–50 mg 3 times a day	1–2 weeks	B
Colchicine	Nonspecific inhibition of the NLRP3 inflammasome	0.5 mg 3 times a day or 0.5 mg if body weight <70 kg	3 months (acute) or 6 months (recurrence)	A
Corticosteroids	Mimicking endogenous effects of cortisol	0.2–0.5 mg/kg of prednisone or an equivalent	2 weeks (acute) or 4 weeks (recurrence)	B
Azathioprine	Blocking purine and DNA synthesis	Up to 2 mg/kg with a slow dosage increase	At least 6 months	C
IVIg	Modulation of adaptative and innate immunity, clearance of infectious agents	400–500 mg/kg intravenously	5 consecutive days but it can be repeated after 1 month	C
Anakinra	Nonselective inhibition of IL-1α and IL-1β	1–2 mg/kg (up to 100 mg) subcutaneously	3–6 months	B

a For all treatments, the attack dose is maintained until symptom resolution and normalization of inflammatory marker levels (eg, C-reactive protein) and other imaging findings (on electrocardiography and echocardiography). Then, dose tapering is recommended by experts. This is of particular importance in the treatment with corticosteroids, in which tapering is slow (eg, a daily dose of prednisone or an equivalent should be reduced by 2.5 mg every 2 to 4 weeks according to case severity, and tapering should be considered on a case-by-case basis).
b Level of evidence: A, based on meta-analyses, >1 randomized controlled trial; B, based on a single randomized controlled trial or nonrandomized observational studies; C, based on case series and expert opinions

Abbreviations: COX, cyclooxygenase; IL, interleukin; IVIg, intravenous immunoglobulin; others, see FIGURE 3

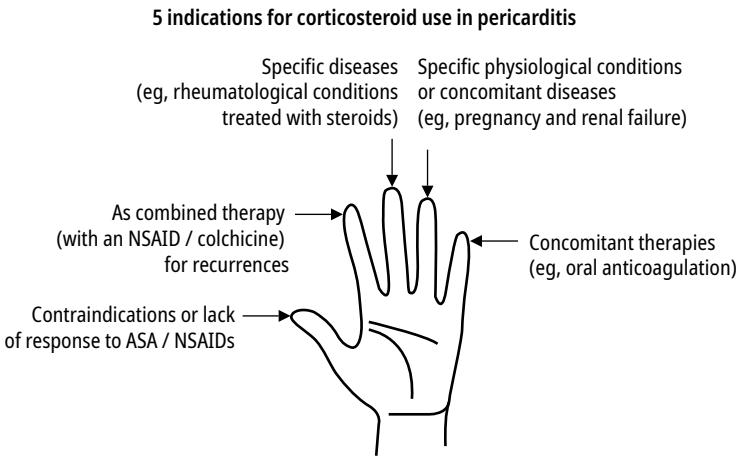


FIGURE 4 Specific indications for administering low-to-moderate doses of corticosteroids as the second-level therapy in pericarditis. Modified from Imazio[38]
Abbreviations: ASA, acetylsalicylic acid; others, see FIGURE 1

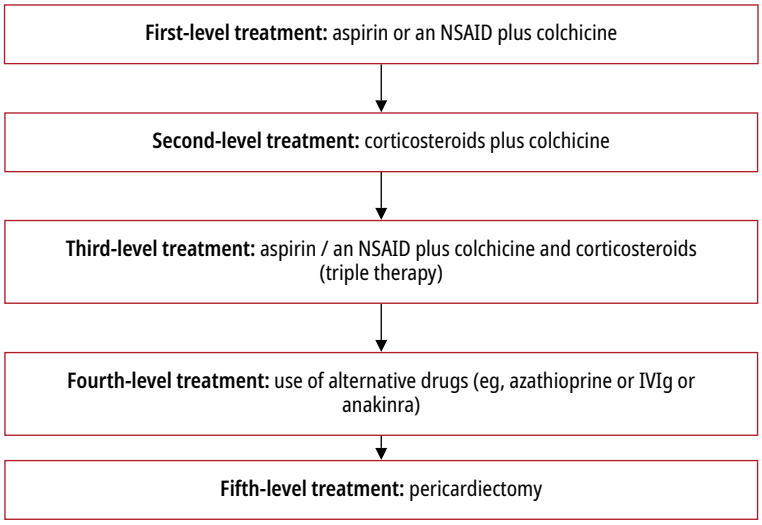


FIGURE 5 Five-level stepwise algorithm for the treatment of pericarditis, based on the current European guidelines[3] and subsequent research on the topic
Abbreviations: see FIGURE 1 and TABLE 4

of cases of noninfectious pericarditis remains "idiopathic" after the search for etiology.[25,26] In these patients, NSAIDs plus colchicine are the cornerstone of medical therapy aimed to control symptoms and prevent recurrences.[3,25-28] Added to NSAIDs, colchicine can halve the recurrence rate in acute or recurrent pericarditis[29-35] (FIGURE 3) and is currently registered in several European countries for this indication (eg, in Italy and Austria). The use of colchicine is a class I and level of evidence A recommendation for the management of acute and recurrent pericarditis according to the 2015 ESC guidelines.[3] In clinical practice, it is important to avoid loading doses and consider those weight-adjusted to reduce possible gastrointestinal side effects, which are the main factors limiting the tolerability of this drug (TABLE 4). Corticosteroid therapy has been associated with an increased risk of recurrences[36] if used early and at high doses; however, there are specific indications for corticosteroid use at low-to-moderate doses (eg, prednisone, 0.2–0.5 mg/kg/d)[37] due to contraindications and nonresponsiveness to NSAIDs, specific diseases already treated with maintenance therapy or with indication for corticosteroids (eg, in vasculitis or systemic inflammatory diseases),[12] concomitant physiological conditions (eg, pregnancy),[39] diseases (eg, renal failure), or therapies (eg, oral anticoagulation) (FIGURE 4).

If the patient does not respond to NSAIDs, colchicine, and corticosteroids, the third level of treatment (FIGURE 5) is represented by triple therapy with a combination of the 3 drugs (a NSAID plus colchicine and a low-to-moderate dose of a corticosteroid).[3,40]

For patients with corticosteroid-dependent pericarditis (unable to taper or withdraw corticosteroids without a new recurrence) and colchicine-resistant pericarditis, 3 alternatives have been suggested in the literature (TABLE 4): azathioprine[41] and human intravenous immunoglobulins[42] for those without systemic inflammation (no fever and / or elevated CRP levels) or anakinra,[43] a nonselective interleukin-1 receptor antagonist (FIGURE 6), particularly recommended for those with systemic inflammation manifested by fever at each recurrence and / or elevated CRP levels. The evidence supporting the use of azathioprine, an old, cheap immunosuppressive drug, and human intravenous immunoglobulins is limited to case reports or small case series.[41,42] On the contrary, there is more evidence in favor of anakinra, based on case series,[43,44] a single randomized controlled trial,[45] and a more recent international registry of treated patients.[46]

Pericardiectomy is the treatment option of last resort in refractory recurrent pericarditis, if all medical therapies have failed.[47]

Risk of complications Recurrence is the most common and troublesome complication of pericarditis, which has been reported in 20% to 30% of patients after the first episode of pericarditis, if not treated with colchicine.[29,33] The recurrence rate is higher in patients with recurrent idiopathic pericarditis (30% to 50%), but can be halved by the regular use of colchicine.[30-32] Other possible complications include cardiac tamponade, which is uncommon (occurs in less than 2% of cases) in the absence of a specific cause, such as cancer.[14,48] Constrictive pericarditis is a complication, which is feared most by clinicians and patients.[49] The common belief is that the risk of developing it is correlated with the number of recurrences: the higher the number of relapses, the higher the risk of constriction.

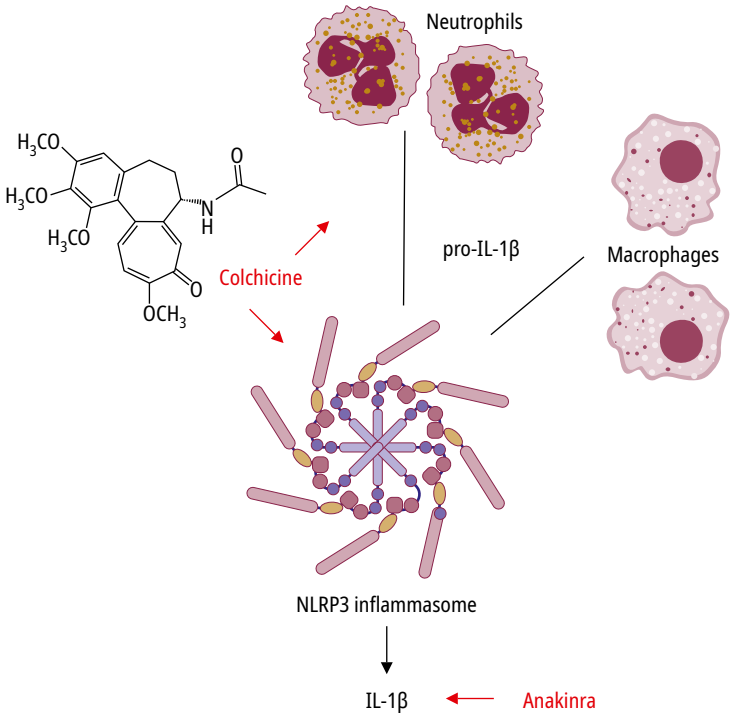


FIGURE 6 Principal mechanisms of action of colchicine and anakinra. Colchicine blocks tubulin polimerization interfering with neutrophils where it is concentrated. Moreover, it is a nonspecific inhibitor of the NLRP3 inflammasome (a cytoplasmatic complex of proteins assembled and activated by inflammatory states responsible for the activation of prointerleukin 1). Anakinra is an antagonist for interleukin-1 beta (IL-β1; the activated form of prointerleukin 1).
Abbreviations: pro-IL, prointerleukin; others, see TABLE 4

However, no cases of constrictive pericarditis have been reported after recurrent idiopathic pericarditis,[50] that is, pericarditis with no identified underlying cause. The risk of developing constrictive pericarditis is related to the cause of pericarditis: low risk (<1%) in patients with idiopathic or viral pericarditis, intermediate risk (3% to 4%) in those with autoimmune diseases, postcardiac injury syndromes, and cancer-related pericarditis, and high risk (20% to 35%) in those with pericarditis of bacterial etiology (especially tuberculous and purulent pericarditis).[48]

Conclusions Pericarditis remains challenging, particularly in its complicated and recurrent forms. Diagnostic and triage criteria have been implemented in clinical practice, which reduced hospitalization and management costs. Recently, current available therapies have been improved by the adjunct of colchicine, and antagonists of interleukin 1, such as anakinra for patients with corticosteroid-dependent and colchicine-resistant pericarditis. However, further research is needed to better elucidate the pathophysiology of recurrences in order to develop more targeted and individualized treatment.

ARTICLE INFORMATION

CONFLICT OF INTEREST MI was a member of the Advisory Board for SOBI and KINIKSA and also received institutional research grants from ACARPIA and SOBI.

HOW TO CITE Imazio M. Noninfectious pericarditis: management challenges for cardiologists. Kardiol Pol. 2020; 78: 396-403. doi:10.33963/KP.15353

REFERENCES

1 Lazaros G, Solomou E, Antonopoulos AS, et al. The landscape of acute pericarditis in Greece: experience from a tertiary referral center. Hellenic J Cardiol. 2019; 60: 139-140.

2 Imazio M, Gaita F, LeWinter M. Evaluation and treatment of pericarditis: a systematic review. JAMA. 2015; 314: 1498-506.

3 Adler Y, Charron P, Imazio M, et al; ESC Scientific Document Group. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: the Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) endorsed by: the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2015; 36: 2921-2964.

4 Imazio M, Gaita F. Diagnosis and treatment of pericarditis. Heart. 2015; 101: 1159-1168.

5 Imazio M, Brucato A, Derosa FG, et al. Aetiological diagnosis in acute and recurrent pericarditis: when and how. J Cardiovasc Med (Hagerstown). 2009; 10: 217-230.

6 Chang SA. Tuberculous and infectious pericarditis. Cardiol Clin. 2017; 35: 615-622.

7 Soler-Soler J, Permanyer-Miralda G, Sagristà-Sauleda J. A systematic diagnostic approach to primary acute pericardial disease. The Barcelona experience. Cardiol Clin. 1990; 8: 609-620.

8 Zayas R, Anguita M, Torres F, et al. Incidence of specific etiology and role of methods for specific etiologic diagnosis of primary acute pericarditis. Am J Cardiol. 1995; 75: 378-382.

9 Reuter H, Burgess LJ, Louw VJ, Doubell AF. The management of tuberculous pericardial effusion: experience in 233 consecutive patients. Cardiovasc J S Afr. 2007; 18: 20-25.

10 Imazio M, Cecchi E, Demichelis B, et al. Indicators of poor prognosis of acute pericarditis. Circulation. 2007; 115: 2739-2744.

11 Gouriet F, Levy PY, Casalta JP, et al. Etiology of pericarditis in a prospective cohort of 1162 cases. Am J Med. 2015; 128: 784.e1-8.

12 Imazio M. Pericardial involvement in systemic inflammatory diseases. Heart. 2011; 97: 1882-1892.

13 Imazio M, Hoit BD. Post-cardiac injury syndromes. An emerging cause of pericardial diseases. Int J Cardiol. 2013; 168: 648-652.

14 Imazio M, Colopi M, De Ferrari GM. Pericardial diseases in patients with cancer: contemporary prevalence, management and outcomes. Heart. 2020; 106: 569-574.

15 Imazio M, Adler Y. Management of pericardial effusion. Eur Heart J. 2013; 34: 1186-1197.

16 Imazio M, Demichelis B, Parrini I, et al. Day-hospital treatment of acute pericarditis: a management program for outpatient therapy. J Am Coll Cardiol. 2004; 43: 1042-1046.

17 Imazio M, Cecchi E, Demichelis B, et al. Myopericarditis versus viral or idiopathic acute pericarditis. Heart. 2008; 94: 498-501.

18 Imazio M, Brucato A, Barbieri A, et al. Good prognosis for pericarditis with and without myocardial involvement: results from a multicenter, prospective cohort study. Circulation. 2013; 128: 42-49.

19 De Filippo O, Gatti P, Rettegno S, et al. Is pericardial effusion a negative prognostic marker? Meta-analysis of outcomes of pericardial effusion. J Cardiovasc Med (Hagerstown). 2019; 20: 39-45.

20 Imazio M, Lazaros G, Valenti A, et al. Outcomes of idiopathic chronic large pericardial effusion. Heart. 2019; 105: 477-481.

21 Imazio M, Brucato A, Maestroni S, et al. Prevalence of C-reactive protein elevation and time course of normalization in acute pericarditis: implications for the diagnosis, therapy, and prognosis of pericarditis. Circulation. 2011; 123: 1092-1097.

22 Imazio M, Pivetta E, Palacio Restrepo S, et al. Usefulness of cardiac magnetic resonance for recurrent pericarditis. Am J Cardiol. 2020; 125: 146-151.

23 Imazio M, Trinchero R. Triage and management of acute pericarditis. Int J Cardiol. 2007; 118: 286-294.

24 Spodick DH. Risk prediction in pericarditis: who to keep in hospital? Heart. 2008; 94: 398-399.

25 Imazio M, Brucato A, Mayosi BM, et al. Medical therapy of pericardial diseases: part I: idiopathic and infectious pericarditis. J Cardiovasc Med (Hagerstown). 2010; 11: 712-722.

26 Imazio M, Brucato A, Mayosi BM, et al. Medical therapy of pericardial diseases: Part II: noninfectious pericarditis, pericardial effusion and constrictive pericarditis. J Cardiovasc Med (Hagerstown). 2010; 11: 785-794.

27 Lotrionte M, Biondi-Zoccai G, Imazio M, et al. International collaborative systematic review of controlled clinical trials on pharmacologic treatments for acute pericarditis and its recurrences. Am Heart J. 2010; 160: 662-670.

28 Chiabrando JG, Bonaventura A, Vecchié A, et al. Management of acute and recurrent pericarditis: JACC state-of-the-art review. J Am Coll Cardiol. 2020; 75: 76-92.

29 Imazio M, Bobbio M, Cecchi E, et al. Colchicine in addition to conventional therapy for acute pericarditis: results of the COlchicine for acute PEricarditis (COPE) trial. Circulation. 2005; 112: 2012-2016.

30 Imazio M, Bobbio M, Cecchi E, et al. Colchicine as first-choice therapy for recurrent pericarditis: results of the CORE (COlchicine for REcurrent pericarditis) trial. Arch Intern Med. 2005; 165: 1987-1991.

31 Imazio M, Brucato A, Cemin R, et al. CORP (COlchicine for Recurrent Pericarditis) Investigators. Colchicine for recurrent pericarditis (CORP): a randomized trial. Ann Intern Med. 2011; 155: 409-414.

32 Imazio M, Belli R, Brucato A, et al. Efficacy and safety of colchicine for treatment of multiple recurrences of pericarditis (CORP-2): a multicentre, double-blind, placebo-controlled, randomised trial. Lancet. 2014; 383: 2232-2237.

33 Imazio M, Brucato A, Cemin R, et al; ICAP Investigators. A randomized trial of colchicine for acute pericarditis. N Engl J Med. 2013; 369: 1522-1528.

34 Imazio M, Brucato A, Forno D, et al. Efficacy and safety of colchicine for pericarditis prevention. Systematic review and meta-analysis. Heart. 2012; 98: 1078-1082.

35 Bayes-Genis A, Adler Y, de Luna AB, Imazio M. Colchicine in pericarditis. Eur Heart J. 2017; 38: 1706-1709.

36 Artom G, Koren-Morag N, Spodick DH, et al. Pretreatment with corticosteroids attenuates the efficacy of colchicine in preventing recurrent pericarditis: a multicentre all-case analysis. Eur Heart J. 2005; 26: 723-727.

37 Imazio M, Brucato A, Cumetti D, et al. Corticosteroids for recurrent pericarditis: high versus low doses: a nonrandomized observation. Circulation. 2008; 118: 667-671.

38 Imazio M. Myopericardial Diseases. New York: Springer; 2016.

39 Brucato A, Pluymaekers N, Tombetti E, et al. Management of idiopathic recurrent pericarditis during pregnancy. Int J Cardiol. 2019; 282: 60-65.

40 Imazio M, Brucato A, Trinchero R, et al. Individualized therapy for pericarditis. Expert Rev Cardiovasc Ther. 2009; 7: 965-975.

41 Vianello F, Cinetto F, Cavraro M, et al. Azathioprine in isolated recurrent pericarditis: a single centre experience. Int J Cardiol. 2011; 147: 477-478.

42 Imazio M, Lazaros G, Picardi E, et al. Intravenous human immunoglobulins for refractory recurrent pericarditis: a systematic review of all published cases. J Cardiovasc Med (Hagerstown). 2016; 17: 263-269.

43 Lazaros G, Imazio M, Brucato A, et al. Anakinra: an emerging option for refractory idiopathic recurrent pericarditis: a systematic review of published evidence. J Cardiovasc Med (Hagerstown). 2016; 17: 256-262.

44 Lazaros G, Vasileiou P, Koutsianas C, et al. Anakinra for the management of resistant idiopathic recurrent pericarditis. Initial experience in 10 adult cases. Ann Rheum Dis. 2014; 73: 2215-2217.

45 Brucato A, Imazio M, Gattorno M, et al. Effect of anakinra on recurrent pericarditis among patients with colchicine resistance and corticosteroid dependence: the AIRTRIP randomized clinical trial. JAMA. 2016; 316: 1906-1912.

46 Imazio M, Andreis A, De Ferrari GM, et al. Anakinra for corticosteroid-dependent and colchicine-resistant pericarditis: the IRAP (International Registry of Anakinra for Pericarditis) study. Eur J Prev Cardiol. 2019 Oct 15. [Epub ahead of print].

47 Khandaker MH, Schaff HV, Greason KL, et al. Pericardiectomy vs medical management in patients with relapsing pericarditis. Mayo Clin Proc. 2012; 87: 1062-1070.

48 Imazio M, Brucato A, Maestroni S, et al. Risk of constrictive pericarditis after acute pericarditis. Circulation. 2011; 124: 1270-1275.

49 Welch TD, Oh JK. Constrictive pericarditis. Cardiol Clin. 2017; 35: 539-549.

50 Imazio M, Brucato A, Adler Y, et al. Prognosis of idiopathic recurrent pericarditis as determined from previously published reports. Am J Cardiol. 2007; 100: 1026-1028.