Curr Cardiol Rep (2016) 18: 50
DOI 10.1007/s11886-016-0727-8

Recurrent Pericarditis: Modern Approach in 2016

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Published online: 23 April 2016

Abstract Recurrent pericarditis is one of the most troublesome complications of pericarditis occurring in about one third of patients with a previous attack of pericarditis. The pathogenesis is presumed to be autoimmune and/or autoinflammatory in most cases. The mainstay of therapy for recurrences is physical restriction and anti-inflammatory therapy based on aspirin or NSAID plus colchicine. Corticosteroids at low to moderate doses (e.g., prednisone 0.2 to 0.5 mg/kg/day) should be considered only after failure of aspirin/NSAID (and more than one of these drugs) or for specific indications (e.g., pregnancy, systemic inflammatory diseases on steroids, renal failure, concomitant oral anticoagulant therapy). One of the most challenging issues is how to cope with patients who have recurrences despite colchicine. A small subset of patients (about 5 %) may develop corticosteroid-dependence and colchicine resistance. Among the emerging treatments, the three most common and evidence-based therapies are based on azathioprine, human intravenous immunoglobulin (IVIG), and anakinra. After failure of all options of medical therapy or for those patients who do not tolerate medical therapy or have serious adverse events related to medical therapy, the last possible option is the surgical removal of the pericardium. Total or radical pericardiectomy is recommended in these cases in experienced centers performing this surgery. A stepwise approach is recommended starting from NSAID and colchicine, corticosteroid and colchicine, a combination of the three options (NSAID, colchicine and corticosteroids), then azathioprine, IVIG, or anakinra as last medical options before pericardiectomy.

Keywords Pericarditis · Recurrence · Therapy · Colchicine · Prognosis

This article is part of the Topical Collection on *Pericardial Disease*

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Introduction

Recurrent pericarditis is one of the most troublesome complications of pericarditis affecting one third of patients after a first attack of pericarditis [1, 2], but in patients with recurrent pericarditis, additional recurrences may occur in up to 50 % of those not treated with colchicine [3, 4, 5••]. Traditional therapy of recurrences was based on anti-inflammatory therapies with the adjunct of colchicine. In this setting, corticosteroids were suggested but are associated with frequent side effects and relapses during the tapering or withdrawal of the drugs [6, 7]. In these cases, patients often develop *corticosteroid-dependence*, that is, recurrences after each attempt to reduce or withdraw corticosteroids.

In the last 10 years, several trials have been published on the efficacy and safety of colchicine for the management of recurrences [1–4, 5••], but also, new therapies have been proposed for more difficult cases not responding to traditional therapies and colchicine [7–9, 10•, 11, 12•, 13•]. In 2015, new guidelines have been issued by the European Society of Cardiology (ESC), and a new algorithm of therapy has been proposed with a stepwise approach [14••].

The aim of the present paper is to review current management of recurrences and new and emerging options for medical and surgical therapy of this condition.

Definitions

Recurrent pericarditis occurs when there is a symptom-free interval from a previous episode of pericarditis. Such time is arbitrarily defined as at least 4 to 6 weeks, considering the duration of the anti-inflammatory therapy for pericarditis and the possible time required by tapering of such therapies [2, 4, 14••]. If symptoms and signs are persisting without a clear free time from disease activity, the term "incessant pericarditis" is preferred [14••, 15, 16]. Such forms may directly progress to constriction and should be recognized in clinical practice [15].

The term "chronic" is generally referred, especially for pericardial effusions and constrictive pericarditis, to disease processes lasting for >3 months, and "chronic pericarditis" is an arbitrary term used by experts for disease lasting >3 months ([14••]; Table 1).

Etiology and Pathophysiology

The etiology of recurrences is poorly understood. Recurrent pericarditis is especially supposed to be immune-mediated in most cases, and this statement is supported by the evidence of non-organ specific autoantibodies and anti-heart antibodies in patients with recurrences [17, 18], as well as response to corticosteroids and colchicine [1–4, 5••, 6, 7].

In addition, recurrences may be caused by an underlying disease (e.g., systemic inflammatory disease, cancer) [18], new or recurrent viral infection (as reported in the Marburg experience in about 20 % of recurrent pericardial effusions) [19], but especially inappropriate treatment of the previous episode of pericarditis (either because of low doses of drugs or too short duration of therapy, or too fast tapering), or missed restriction of physical activities (Table 2) [20–22].

A specific subgroup of recurrences is related to an autoinflammatory disease, especially in children [23, 24]. Autoinflammatory diseases are characterized by periodic activation of the innate immune system for unknown reasons. Such activation is responsible for intense episodes of inflammation that may result in fever, pericarditis, rash, and/or joint swelling. These diseases also carry the risk of amyloidosis as a consequence of chronic and/or recurrent inflammation. The two most common diseases that have been reported to be associated with recurrent pericarditis include *Familial Mediterranean Fever (FMF)* and *Tumor Necrosis Factor (TNF) Receptor-Associated Periodic Syndrome (TRAPS)*.

FMF is an autosomal recessive inherited disease caused by mutations of the MEFV gene located on short the arm of chromosome 16. FMF usually begins in childhood and occurs most commonly in people of Jewish, Armenian, Arab, and Turkish backgrounds. As many as 1 in 200 people in these populations have the disease. Patients with familial Mediterranean fever (FMF) suffer from recurring bouts of fever, most commonly with severe abdominal pain due to inflammation of the abdominal cavity (peritonitis), and possible additional serositis including pericarditis. Attacks can also include arthritis, pleuritis, and skin rashes [25].

TRAPS, formerly known as familial Hibernian fever, is a rare autosomal dominant autoinflammatory disorder characterized by recurrent episodes of long-lasting fever and inflammation in different regions of the body. It is characterized by long, dramatic, episodes of high fever, severe pain in the abdomen, chest, or joints, skin rash, and inflammation in or around the eyes. The age of onset varies from early childhood to adulthood, and the disease appears to affect men and women equally. The earliest cases of TRAPS were reported in individuals of Irish-Scottish descent, but the disease has since been found in nearly all ethnic groups.

TRAPS is caused by a genetic defect in a protein known as tumor necrosis factor receptor (TNFR). Mutant TNFRs promotes inflammation. Episodes can be triggered by infection or stress. The disease is now managed with anti-interleukin (IL)-1 antagonists, rather than corticosteroids or tumor necrosis factor (TNF) inhibitors [26].

Table 1 Definitions of recurrent, incessant, and chronic pericarditis

	Definition
Incessant	Pericarditis lasting for > 4 to 6 weeks but <3 months* without remission
Recurrent	Recurrence of pericarditis after a documented first episode of acute pericarditis and a symptom-free interval of 4–6 weeks or longer°
Chronic	Pericarditis lasting for >3 months*

*Arbitrary term defined by experts

°Usually recurrences occur within 18 to 24 months from the index attack

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Table 2 Common causes of recurrent pericarditis

Cause	Frequency
Idiopathic	>60 %
Infectious (e.g., especially viral)	About 20 %
Systemic inflammatory diseases and pericardial injury syndromes	10–25 %
Autoinflammatory diseases	About 5–10 %*
Neoplastic pericardial diseases	5–10 %
Inadequate treatment of the first or subsequent attack of pericarditis	Unknown°

*Especially in children

°Inadequate treatment according to doses, duration, and tapering and may include the lack of an adequate time of restriction of physical activities

Diagnosis

The diagnosis of recurrent pericarditis is based on an established evidence of a previous attack of acute pericarditis plus "pericarditic pain" and another objective evidence of activity of pericardial inflammatory disease (e.g., pericardial rubs, ECG changes, new or worsening pericardial effusion, elevation of markers of inflammation or white blood cell count) [3, 5••]. In atypical or doubtful cases, the evidence of pericardial inflammation by an imaging technique is helpful (e.g., pericardial contrast enhancement on CT or evidence of edema and delayed enhancement on CMR) (Table 3) [14••, 27••, 28•].

In patients with recurrences, the diagnostic evaluation is essentially based on (1) confirmation of the diagnosis, (2) evaluation of possible risk factors for complications (e.g., especially moderate to large pericardial effusions or worsening pericardial effusions, cardiac tamponade, incomplete or lacking response to anti-inflammatory therapy), and (3) exclusion of potential specific etiologies (e.g., tuberculosis, systemic inflammatory diseases, cancer) that could be missed in the evaluation of previous episodes of pericarditis [21].

The same high-risk features or red flags presented for acute pericarditis should be considered in patients with recurrent pericarditis. If there are no risk factors and no clues or suspicion of a missed etiology, there is no reason to repeat etiological diagnostic tests for each recurrence [29–31]. There is increasing work suggesting the importance of the assessment of systemic inflammation by C-reactive protein or pericardial inflammation by an imaging technique, especially cardiac magnetic resonance (CMR) to monitor therapy and assess its individualized duration. Also tapering of anti-inflammatory therapies is recommended in an attempt to reduce the risk of subsequent recurrences according to experts opinion [14••].

Table 3 Diagnostic criteria for incessant, recurrent and chronic pericarditis

Incessant pericarditis is pericarditis lasting for > 4 to 6 weeks but <3 months* without remission.

Recurrent pericarditis is defined with:

(1) a documented first attack of acute pericarditis,

(2) a symptom-free interval of 4 to 6 weeks or longer*, and

(3) evidence of subsequent recurrence of pericarditis documented by recurrent pain compatible with pericarditis and one or more of the following signs:

a pericardial friction rub,

changes on electrocardiography,

echocardiographic evidence of new or worsening pericardial effusion,

elevation in the white-cell count, erythrocyte sedimentation rate, or C-reactive protein (CRP) level.

Chronic pericarditis is pericarditis lasting for >3 months*

*3 months is an arbitrary time interval defined by experts and reflect the usual resolution of an acute attack of pericarditis within this time interval; recurrences usually occur within 18–24 months, but a precise upper limit of time has not been established

Traditional Anti-Inflammatory Therapy

The mainstay of therapy for recurrences is physical restriction as non-pharmacological measure until symptoms resolution and C-reactive protein normalization [32] and anti-inflammatory therapy based on aspirin or NSAID plus colchicine as first choice for acute pericarditis (Table 4) [14••, 33]. Corticosteroids should be considered only after failure of aspirin/NSAID (and more than one of these drugs) [32].

Corticosteroids should be considered also for specific indications including (1) a systemic inflammatory disease already on maintenance therapy with steroids or with an indication to steroids, (2) pregnancy, (3) renal failure, and (4) need to avoid NSAID for concomitant anticoagulant therapies.

High doses of corticosteroids (e.g., prednisone 1 to 1.5 mg/kg/day) are no longer recommended [14••] since may increase the risk of severe side effects and thus drug withdrawals, hospitalizations, and even more recurrences probably related to such events [6, 7, 34].

In patients on steroids, it is critical to use low to moderate doses (e.g., prednisone 0.2 to 0.5 mg/day or equivalent) for 2 to 4 weeks according to the clinical response

Table 4 Common therapeutic options for recurrent pericarditis

Therapy	Dosing	Duration*	Tapering	Monitoring	LOE
Aspirin	750–500 mg three times daily	1–2 weeks	Weekly in 3–4 weeks	Needed	A
Ibuprofen	600–800 mg three times daily	1–2 weeks	Weekly in 3–4 weeks	Needed	A
Indomethacin	50 mg three times daily	1–2 weeks	Weekly in 3–4 weeks	Needed	B
Colchicine	0.5 once (<70 kg or chronic kidney disease) or 0.5 mg twice daily°	6 months	May be considered	Needed	A
Prednisone	0.2 to 0.5 mg/kg/day	2–4 weeks	Several months	Needed	B
Azathioprine	Starting with 1 mg/kg day then gradually increased to 2–3 mg/kg/day	Several months	Several months	Needed	C
IVIG	400 to 500 mg iv daily for 5 days	5 days	Not required	Needed	C
Anakinra	1 to 2 mg/kg/day up to 100 mg/day in adults	Several months	To be determined	Needed	C
Pericardiectomy	n.a.	n.a	n.a	Needed	C

Monitoring is essentially based on the assessment of blood count, creatinine, creatine kinanse (CK), transaminases, C-reactive protein, and echocardiography

LOE A, data derived from multiple randomized clinical trials or meta-analyses; LOE B, data derived from a single randomized clinical trial or large non-randomized studies; and LOE C, consensus of opinion of the experts and/or small studies, retrospective studies, and registries

IVIG IV immuno globulins, *n.a.* not applicable

*Therapy duration as initial dosing

°0.6 mg is the usual dosing that is available in North America

and then slow tapering the drug after symptoms resolution and normalization of C-reactive protein (Table 5) [7, 33]. In case of recurrence of symptoms during steroid tapering, that is very common at doses below 15 mg/day of prednisone or equivalent, do not increase the corticosteroid again, but try to control the disease increasing or reinstituting aspirin or a NSAID plus colchicine [14••, 35].

In more difficult cases, it is possible to combine either NSAID plus colchicine and low to moderate doses of corticosteroids in an attempt to better control symptoms [14••].

Colchicine

Colchicine is now a well-established first option for the therapy of acute and recurrent pericarditis. Based on several clinical trials [1, 5••], colchicine is indicated to hasten the response to additional anti-inflammatory therapies (e.g., NSAID, corticosteroids), improve remission rates at 1–2 weeks, and especially reduce the risk of recurrences by at least 50 %. The drug is recommended at low doses (0.5 mg BID for patients >70 kg or only 0.5 once daily for 6 months) without a loading dose in order to improve the compliance of the patients and reduce the

Table 5 Tapering of corticosteroids in recurrent pericarditis

Prednisone dose*	Starting dose 0.25 to 0.50 mg/kg/day*	Tapering**
Prednisone daily dose	>50 mg	10 mg/day every 1 to 2 weeks
	50–25 mg	5–10 mg/day every 1 to 2 weeks
	25–15 mg	2.5 mg/day every 2 to 4 weeks
	<15 mg	1.0 to 2.5 mg/day every 2 to 6 weeks

Calcium intake (supplement plus oral intake) 1,200–1,500 mg/day and vitamin D supplementation 800-1000 IU/day should be offered to all patients receiving glucocorticoids. Moreover, bisphosphonates are recommended to prevent bone loss in all men ≥50 years and postmenopausal women in whom long-term treatment with glucocorticoids is initiated at a dose ≥5.0-7.5 mg/d of prednisone or equivalent

*Avoid higher doses except for special cases, and only for a few days, with rapid tapering to 25 mg/day. Prednisone 25 mg is equivalent to methylprednisolone 20 mg

**Every decrease in prednisone dose should be done only if the patient is asymptomatic and C-reactive protein is normal, particularly for doses <25 mg/day

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risk of gastrointestinal intolerance, the most common side effect (reported in about 5-10 % of cases).

The use of colchicine received a Class I recommendation, LOE A in 2015 ESC guidelines [14••].

New Emerging Options for Medical Therapy

One of the most challenging issues is how to cope with patients who have recurrences despite colchicine. A small subset of patients (about 5 %) may develop corticosteroid-dependence and colchicine resistance (that is still having recurrences despite colchicine and triple therapy with NSAID, colchicine, and corticosteroids).

Among the most promising old and new emerging treatments, the three most common and evidence-based therapies are based on azathioprine, human intravenous immunoglobulin (IVIG), and anakinra (Table 4) [8, 9, 10•, 11, 12•, 35]. The main mechanism of action of each drug is reported in Fig. 1.

Azathioprine

Azathioprine is an immunosuppressive drug belonging to the chemical class of purine analogs that is commonly used in organ transplantation recipients and autoimmune diseases. The largest reported experience is a single-center, retrospective study of 46 patients with idiopathic recurrent pericarditis (mean age 40 years, range 11 to 71 years), where azathioprine was administered at the dose of 1.5–2.5 mg/kg die for 13.6 ±5.1 months in the idiopathic forms. The use of azathioprine was associated with stable remission following steroid discontinuation in more than 50 % of patients [8]. Overall azathioprine was well-tolerated in the mentioned study; transient hepatotoxicity was observed in about 10 % of cases and leukopenia in 6–7 %; transient gastrointestinal symptoms with spontaneous resolution were reported in 4–5 % of cases.

NSAIDs and corticosteroids may be combined and continued, and the drug is especially a steroid-sparing agent to reduce and withdraw corticosteroids with a slow onset of action (1-2 months) that requires a prolonged therapy of several months [14••].

Overall, azathioprine is a potentially useful, cheap, and safe solution in patients who do not respond to conventional therapies and are not able to withdraw corticosteroids (LOE C) [14••]. Azathioprine is essentially a steroid-sparing agent; it is less useful in the resolution of an acute attack. The recommended initial dosage is 1 mg/kg/day given once daily, gradually increased till 2–3 mg/kg/day. Concomitant therapy with allopurinol greatly increases bone marrow toxicity and must be avoided [14••].

Intravenous Immunoglobulins (IVIG)

IVIGs are prepared from plasma pooled from healthy donors. Administered IVIGs can exert both anti-inflammatory and immunomodulatory effects; moreover, they may be helpful for the clearance of infectious agents [35]. This treatment has been studied both in children and adults with recurrent pericarditis with limited published data [9, 10•]. The used treatment scheme is 400 to 500 mg/kg/day for 5 days. Overall, IVIGs are a possible rapidly acting, safe, and efficacious steroid-sparing treatment for refractory pericarditis (LOE C), useful in the management of the acute attack;

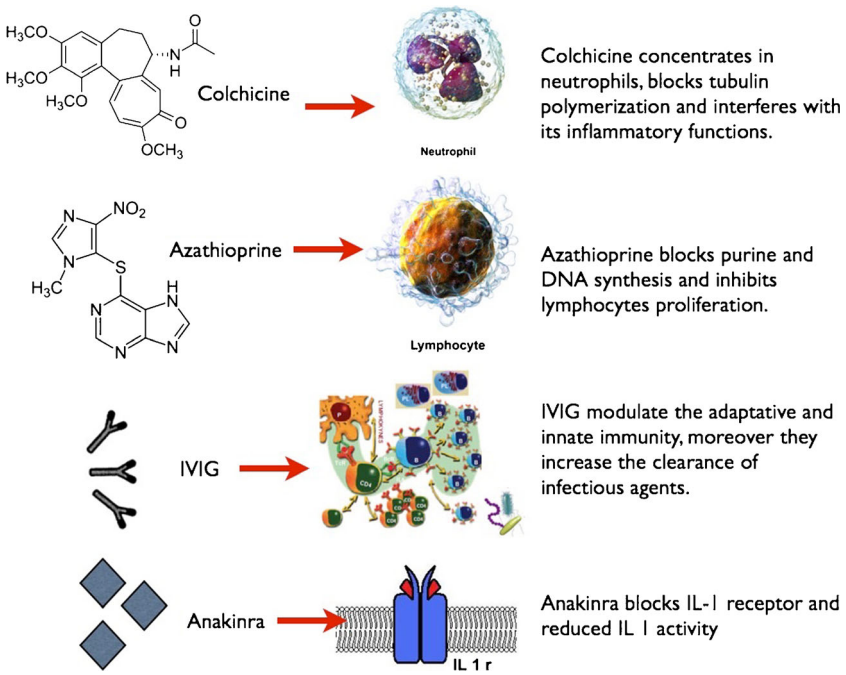

Fig. 1 Mechanisms of actions of drugs in recurrent pericarditis

recurrences may occur after IVIG discontinuation but a cycle of therapy can be repeated after 1 month [35]. The main limitations of this treatment are represented by the costs and possible safety concerns related to the need of administration of plasma derivate from "healthy donors" [35].

Anakinra and Biological Agents

Anakinra is a recombinant form of the naturally occurring interleukin-1 (IL-1) receptor antagonist that has been successfully used in patients with FMF after colchicine failure. It essentially acts by antagonizing the biological effects of IL-1, which is a proinflammatory cytokine [12•, 25]. It is currently approved by the Food and Drug Administration for the treatment of rheumatoid arthritis. The drug has been initially used in pediatric patients, where the long-term side effects of corticosteroids are particularly relevant, such as the deleterious effects on growth, and also in adult patients with refractory recurrent pericarditis, especially if corticosteroid-dependent [11, 12•]. Anakinra is a potentially useful, effective, rapidly acting steroid-sparing agent (LOE C) [14••]. However, recurrences after drug discontinuation are a matter of concern, and the drug is rather expensive. RCTs are required to confirm these findings and address the most effective treatment protocol [12•]. Currently it is usually prescribed as 1 to 2 mg/kg/day up to 100 mg sc in adults for 6 months then tapered. The best treatment scheme is to be determined.

After failure of all options of medical therapy or for those patients who do not tolerate medical therapy or have serious adverse events related to medical therapy, the last possible option is the surgical removal of the pericardium. Total or radical pericardiectomy is recommended in these cases in experienced centers performing this surgery [13•] Often, this is done as a last resort after exhausting medical therapy in younger patients who have a lot of adverse effects from drugs (especially steroids).

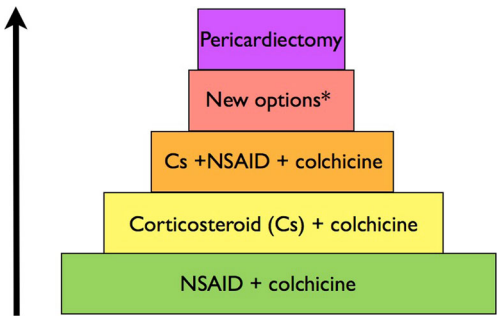

Fig. 2 A proposed stepwise approach for therapy of recurrent pericarditis. The *arrow* indicates the direction of the stepwise approach from NSAID/aspirin towards pericardiectomy after failure of all medical therapies. *Includes azathioprine, IVIG, and anakinra

Prognosis

The overall prognosis of idiopathic recurrent pericarditis (the most common type of recurrence occurring in clinical practice) is good. Despite a possible impairment of the quality of life for a limited time of a few years (usually 1–2 years) with several recurrences, there is no significant risk of increased mortality or chronic evolution [36]. Constrictive pericarditis has never been described or published in the literature [37]; however, a subset may have transient constrictive physiology on imaging. The risk of constriction is related to the etiology and not the number of recurrences [38]. Moreover, in the absence of a missed etiology, also the risk of cardiac tamponade is very low in idiopathic recurrent pericarditis [37–39].

Conclusions

The management of recurrent pericarditis is one of the most difficult tasks of "Pericardiology". A stepwise approach is recommended according to 2015 ESC guidelines (Fig. 2) starting from the common and cheaper options (i.e., NSAID and colchicine), then corticosteroid and colchicine, a combination of the three options (NSAID, colchicine, and corticosteroids), azathioprine, IVIG, or anakinra as last medical options before pericardiectomy [40].

Compliance with Ethics Guidelines

Conflict of Interest Dr. Imazio's institution has received research grants from Acarpia srl (Madeira, Portugal) and SOBI (Stockholm, Sweden). Drs Imazio, Adler, and Charron have been members of the Task Force for 2015 ESC guidelines on pericardial diseases.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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