

# Recurrent Pericarditis

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*Gurpreet Singh Wander, Shibba Takkar Chhabra*

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**R**elapsing or recurrent pericarditis is probably the most troublesome complication of acute pericarditis, and represents one of the greatest therapeutic challenges among the disorders of the pericardium.

It occurs in 15% to 32% of cases and the cause of the recurrence is usually unknown, although in some cases it may be traced to viral infection or may be a consequence of coronary artery bypass grafting<sup>1</sup>. The optimal method for prevention has not been fully established; accepted modalities include nonsteroidal anti-inflammatory drugs, corticosteroids, colchicines, immunosuppressive agents, and pericardiectomy. In present review, we discuss the aetiopathogenesis, clinical manifestations, prognosis and management of recurrent pericarditis.

## DEFINITION

The term relapsing pericarditis includes two clinical types, the incessant type and the intermittent type of recurrent pericarditis.

### Incessant type of recurrent pericarditis

The term incessant applies to those patients in which discontinuation or attempts to wean from anti-inflammatory treatment nearly always ensures a relapse in a period of less than six weeks.<sup>2</sup> This situation can be seen after discontinuation of the usual anti-inflammatory drugs (aspirin, indomethacin, or ibuprofen) but is particularly frequent and worrying in patients on steroids. Some of these patients may be said to be "steroid hooked" and, in fact, these patients can show a threshold level of prednisone treatment (usually between 10-20 mg) below which relapse

is probable.

### Intermittent type of recurrent pericarditis

The term intermittent refers to those patients with symptom-free intervals conventionally longer than six weeks without treatment.

### Historical review

The possibility of recurrences was already recognized in early descriptions of acute pericarditis. Their frequency in clinical series including more than 40 patients varies between 8-80% (average 24%), with no distinction between incessant and intermittent types. Relapses of 15%, 23% and 32% are reported in three largest series of patients with idiopathic pericarditis. In post traumatic, post infarction and post pericardiectomy pericarditis, no precise figure can be given, but recurrence is common.<sup>3</sup> In Dressler's experience, recurrences were the rule in post myocardial infarction syndrome; 35 of 44 cases had at least one relapse. Robinson and Brigden described recurrences in 17 of 20 patients with idiopathic pericarditis, in 4 of 5 with post infarction pericarditis, and in 12 of 16 with post cardiectomy syndrome.

## AETIOLOGY AND AETIOPATHOGENESIS

The possible causes of relapsing pericarditis (Table I) are discussed as follows:

- 1. Viral:** The most typical form of relapsing pericarditis occurs after a first episode of idiopathic benign pericarditis, presumably of viral origin. The viruses most frequently implicated are enterovirus, mainly coxsackie B. Higher concentrations of immunoglobulin IgM antibodies have been found in patients with relapses, which can express a persistent viral antigenic stimulation due to persistent viral

**Table 1. Possible causes of relapsing pericarditis**

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- Idiopathic pericarditis
  - Viral pericarditis
  - Post-myocardial and pericardial injury syndromes
    - Post-myocardial infarction syndrome
    - Post-pericardiotomy syndrome
    - Post-traumatic pericarditis
  - Vasculitis-connective tissue diseases
  - Other (very rare)
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infection or new exposure to viral illness.

**2. Autoimmune:** Autoimmune responses can certainly play a role in the pathogenesis of recurrent idiopathic or postviral pericarditis.

**3. Inadequate anti-inflammatory treatment of the index attack** can explain the relapses in some cases. However, there is no consensus about the optimal duration of treatment and the appropriate doses of the drugs.

**4. Corticosteroid treatment in the index attack:** French authors have suggested that corticosteroid treatment given in the index attack can favour the occurrence of relapses because of their deleterious effect of viral replication. In the series of Raatikka and colleagues the mean number of relapses in steroid treated patients was much higher than those not so treated (8.3 v 4.5), during a follow up period of four years.

**5. Post-myocardial and postpericardial injury syndromes:** Relapsing pericarditis can also occur in the post-myocardial and postpericardial injury syndromes; relapses after open heart surgery seem to be more frequent in children and adolescents, especially after atrial septal defect closure. An immunopathologic mechanism is probably the cause of these relapses as anti-heart antibodies have been found in some cases.

**6. Genetic:** Genetic factors may play a role in the development of a relapse as well. Unlike idiopathic recurrent pericarditis, these cases may eventually evolve to constrictive pericarditis (this especially occurs in those patients who suffer a tamponade caused by haemopericardium in the index attack).

**7. Vasculitis-connective tissue disease:** An immunopathologic mechanism seems to be evident in the relapsing pericarditis of vasculitis-connective tissue disease, especially disseminated lupus erythematosus.

**8. Infections:** Infectious pericarditis caused by specific agents, such as bacterial and tuberculous pericarditis, usually have a subacute or a protracted chronic course with unremitting symptoms, even on common anti-inflammatory

drugs. However, they do not present with a true picture of relapsing pericarditis with intervals of symptom-free periods.

**9. Neoplastic:** Neoplastic pericarditis can show an oscillating clinical course, and, occasionally, apparently self limited pericarditis with subsequent reappearance of pericardial manifestations. However, patients with pericardial malignancies, either primary or metastatic, usually have a very poor prognosis, with no propensity for reoccurrence or chronicity to become manifest.

In summary, the most frequent causes of relapsing pericarditis are idiopathic or viral pericarditis and post pericardial injury syndromes. In patients without previous cardiac surgery, and in whom connective tissue disease has been ruled out, relapsing-intermittent pericarditis with symptom-free periods longer than six weeks makes the diagnosis of idiopathic/viral pericarditis practically certain.

#### CLINICAL MANIFESTATIONS

Recurrent pericarditis often has the features of a systemic inflammatory disease, particularly at the onset. Pleuropulmonary involvement occurs in one third of adults and in two thirds of pediatric patients, and liver involvement is seen in 8%.

Although the clinical manifestations during recurrences are similar to the first episode of pericarditis, the pattern of relapsing pericarditis is quite characteristic in that the index attack usually is the most severe, while subsequent episodes are milder. In particular, objective manifestations of pericarditis such as pericardial friction rub, electrocardiographic changes, and pericardial effusion are clearly less frequent in subsequent episodes than in the index attack, so in some patients the clinical manifestations in relapses are limited to “pericardial” pain only. For example, in the historical series by Fowler and Harbin<sup>4</sup> that included 31 patients with recurrent acute pericarditis, all patients had pericardial friction rub and evidence of pericardial effusion or characteristic electrocardiographic changes in the index attack, while these manifestations were entirely absent in subsequent relapses in seven patients. In these patients the evidence of pericarditis (apart from pericardial pain) was provided by an increased erythrocyte sedimentation rate, white blood cell count, or fever. This clinical pattern may occasionally result in diagnostic problems in anxious patients reporting chest pain without other features. In one series<sup>5</sup>, pericardial effusion was present in all 15 patients in the first recurrence, but

its frequency decreased progressively with the subsequent relapses; a similar pattern was followed by the ECG changes. If significant pericardial effusion is not present in the index attack, it is very unlikely that it develops in subsequent recurrences. This is also true for clinical tamponade that is rare in recurrent pericarditis. The number of recurrences and the interval between the episodes vary among patients and are not predictable in individual cases, except during corticosteroid weaning as some patients clearly seem to have a threshold level for recurrences. In an experience with 44 patients with recurrent pericarditis (none had received steroids during the index episode)<sup>6</sup>, 20 patients had two episodes, 19 patients had three to five episodes, and five patients had more than five episodes, so although recurrences are relatively common, the number of patients with multiple episodes is much lower.

### PROGNOSIS

A common misconception among physicians and fear among patients is that repeated pericardial inflammation may lead to constrictive pericarditis or cardiomyopathy but, in the majority of patients, recurrent attacks of chest pain are the only major disabling feature of the disease. In fact, the hallmark of recurrent pericarditis is the combination of two opposite facts: on the one hand, the excellent life prognosis with exceedingly rare severe complications, and, on the other hand, the severe impairment of the quality of life in some patients caused by incessant recurrences. As previously mentioned, tamponade is very rare during recurrences, especially when not present in the index attack. In the series by Fowler and Harbin<sup>4</sup> tamponade was present in the initial attack in three patients, but in none of the recurrences. Cardiac tamponade was also reported in series by Robinson and Bridgen (4 of 33 patients) and Clementy et al. (2 of 20 patients). Although constrictive pericarditis may occur in about 1% of patients with acute idiopathic pericarditis<sup>7</sup>, it is not a complication of recurrent pericarditis in spite of numerous episodes. Similarly, in the 120 patients in the COPE trial, not a single case of constrictive pericarditis or cardiomyopathy was reported. Myocardial disease is also not a finding of relapsing pericarditis. In the series by Fowler and colleagues, no patient developed chronic myocardial disease as documented by cardiac dilation, gallop rhythm or cardiac dysfunction, and no patient had cardiac arrhythmias or conduction disturbances.

### RECURRENT PERICARDITIS - SPECIFIC ETIOLOGIES

#### Viral pericarditis

Viral pericarditis is often overlooked in clinical practice.

Most cases of acute pericarditis and up to one third of recurrent cases are because of viral infections. A definite diagnosis would require analysis of pericardial fluid or tissue, while serology and other cultural studies (i.e. throat and rectal swabs) are not reliable and diagnostic; even a fourfold rise in serum antibody levels or evidence of specific antiviral IgM is suggestive of a recent systemic infection, but not specifically diagnostic for pericarditis. A definite diagnosis is often missing, but fortunately these cases are generally self-limiting and can be treated with aspirin or a non-steroidal anti-inflammatory drug. As a precise diagnostic definition is not necessary and does not alter management, most cases are not investigated and thus are labeled as idiopathic in clinical practice. Obviously, a comprehensive and invasive approach including systematic evaluation of pericardial fluid and tissue may be able to reduce these 'idiopathic' cases, but this approach is usually not warranted or available in routine clinical practice, and more sophisticated diagnostic techniques including PCR for the detection of viral genome may be considered especially for research purposes.

#### Tuberculous pericarditis

Tuberculous pericarditis represents about 5% of unselected patients with acute pericarditis from developed countries, but more than 60% of patients from developing countries. It usually develops by retrograde lymphatic spread from peritracheal, peribronchial or mediastinal lymph nodes or by haematogenous spread from a primary tuberculous infection. The early lymphatic involvement is the reason for the common presence of pericardial effusion. Echocardiographical findings are non-specific, but the effusion is usually moderate to large, moreover cardiac tamponade, fibrinous strands, echo dense exudates and pericardial thickening are commoner than in viral or 'idiopathic' cases.

Tubercular pericarditis in endemic areas especially in the scenario of increasing incidence of HIV positive patients is prone to several relapses. The incidence of recurrent or persistent tubercular pericarditis (Table II) in the IMPI registry was found to be 18%. 15.1% & 5.4% of patients developed effusive constrictive and constrictive pericarditis respectively. Hence, the principles of management of tubercular pericarditis in definite as well as probable cases should be adhered to prevent recurrence. Complete drainage of pericardial fluid, strict adherence to anti-tubercular treatment and ruling out drug resistance is required in patients with definite tubercular pericarditis (Table III). In probable cases, diagnosis of tuberculosis should

**Table II. Definition: Recurrent or Persistent TB Pericarditis**

- **Recurrent tuberculous pericarditis:**
  - Patient has re-accumulation of pericardial effusion with signs and symptoms of pericardial disease after drainage or initial resolution with treatment.
- **Persistent tuberculous pericarditis:**
  - Failure of signs and symptoms and pericardial effusion to resolve or even worsening with or without tamponade despite proven compliance with anti-tuberculosis medication.

**Table III. Principles of Management of Recurrent or Persistent TB Pericarditis**

- **Definite or proven TB pericarditis:**
  - Verify adherence with anti-tuberculosis treatment (DOTS)
  - Rule out drug resistant organisms
  - Complete drainage of pericardial fluid (open or percutaneous)
  - Continue with anti-tuberculosis chemotherapy
- **Probable or presumed TB pericarditis:**
  - Pursue the diagnosis of TB by all means possible including PCR
  - Exclude an alternative diagnosis
  - Complete drainage of pericardial fluid
  - Continue with trial of anti-tuberculosis chemotherapy until proven otherwise

be pursued by all means (including PCR) and alternative diagnosis should be ruled out.

#### **NEOPLASTIC PERICARDITIS**

Neoplastic pericarditis is also an important specific diagnosis to rule out in patients with pericarditis. Despite a higher frequency in selected patients, neoplastic pericarditis is responsible for about 5% of unselected patients of acute pericarditis and may be sometimes the cause of recurrences. Virtually, any malignant tumour can metastasise to the pericardium, with the most common being lung and breast cancer and lymphomas. Lung cancer is the commonest malignancy giving early invasion of lymphatic nodes and thus being easily responsible for pericardial effusion. Primary tumours of the pericardium are less common. Important among them is the highly malignant mesothelioma, which can be extensive. Even in large case series, only 40-55% of patients with known malignancy and pericardial effusion could be confirmed (by cytology or histology) to have

malignant pericarditis. The remaining causes included radiation, infection, haemorrhage and idiopathic.

In a report of 450 consecutive patients, neoplastic aetiology was found in 33 of 450 patients with acute pericardial disease (7.3%). Risk factors for a neoplastic aetiology were a history of malignancy [odds ratio (OR) 19.8], cardiac tamponade at presentation (OR 7.0), a lack of response to non-steroidal anti-inflammatory drugs and recurrent or incessant pericarditis (OR 10.0). Thus, a detailed evaluation, including a search for occult malignancy, should generally be reserved for patients who have persistent or recurrent pericarditis that is unresponsive to anti-inflammatory therapy, and those who present with a new large pericardial effusion or cardiac tamponade.

#### **DIAGNOSIS**

Relapsing pericarditis, with well defined clinical episodes and symptom-free periods longer than six weeks, does not raise special diagnostic difficulties. In patients with no previous cardiac surgery or myocardial infarction, no specific diagnostic test needs to be done. Once the possibility of collagen vascular disease has been ruled out, relapsing pericarditis is nearly always of viral/immunologic origin, so additional investigations are irrelevant from a practical point of view.

In autoimmune pericarditis that fails to respond to NSAID therapy and has frequent recurrence, diagnostic modalities require that antisarcolemmal antibodies should be present, polymerase chain reaction for cardiotropic viruses and other infectious agents should be negative, and immunoglobulin M against these agents should not be detectable. In addition, tissue should be examined after immunocytochemical and immunohistochemical staining. However, these modalities are very costly and still remain an investigational tool.

Studies<sup>8</sup> have revealed that “diagnostic” pericardial tap and biopsy seldom yield the cause, whereas paradoxically, when these procedures are performed for conditions such as tamponade and suspected purulent infection or neoplastic disease, the diagnostic yield is much improved. These important studies have strongly influenced clinical practice by sharply decreasing the frequency of invasive investigation and hospitalization for uncomplicated acute pericarditis. When it appears doubtful that a patient has viral (or idiopathic) pericarditis, or has a complication such as cardiac tamponade, or fails to respond to standard anti-inflammatory treatment, hospitalization for treatment such as pericardiocentesis, and comprehensive investigation of

causation are mandatory. Pericardioscopy and the PerDUCER, an instrument developed to invade the pericardium when effusion is not present, is not available in most major medical centers and has limited role in diagnosis.

## TREATMENT

The patients of recurrent pericarditis may generally be

**Table IV. Clinical Poor Prognostic Predictors\* for Pericarditis**

### Major

- Fever >38°C
- Sub acute onset
- Large pericardial effusion
- Cardiac tamponade
- Lack of response to aspirin or NSAIDs after at least 1 wk of therapy

### Minor

- Myopericarditis
- Immunodepression
- Trauma
- Oral anticoagulant therapy

treated as outpatient unless poor prognostic predictors (Table IV) are present or a specific cause can be ruled out. The two main goals of therapy are the treatment of acute episodes and the prevention of subsequent recurrences. The treatment modalities include anti-inflammatory therapy - Corticosteroids, NSAIDs, Aspirin & Colchicine. Interventional techniques like pericardiectomy, pericardial window and intra pericardial administration of triamcinolone have limited role. Several drugs (Azathioprine, Cyclophosphamide, Cyclosporine, Methotrexate, Hydroxychloroquine, Intravenous immunoglobulin, Anakinra) have been used in management of refractory cases. These treatment modalities are discussed as follows.

### Corticosteroids

Although reviews and guidelines suggest limiting the use of corticosteroids in inflammatory pericardial syndromes to patients with intolerance, contraindications, or real failure of aspirin and other NSAIDs, these drugs are widespread in general practice, especially for recurrent cases, and the majority of patients with recurrent pericarditis are treated with corticosteroids. The main reason for their success is that corticosteroids are able to induce a quick response with symptom control and initial remission. Nevertheless, the treatment often is quickly tapered because of the fear of possible side effects, and relapses and severe side

effects related to the need of prolonged treatment are common. Moreover, they are recognized as a risk factor for recurrences, probably because of impaired virus clearance. Thus, a troublesome issue is how to manage a patient with recurrent pericarditis and corticosteroid dependence.

The evidence to support the use of corticosteroids for pericarditis is rather weak. Specific data come from only 1 retrospective study on recurrent pericarditis. In this study, 12 patients with recurrent pericarditis unrelated to any systemic disease were treated for 3 months with high-dose prednisone (1.0 to 1.5 mg/kg/d) for 1 month with subsequent gradual tapering. When prednisone tapering was started, all patients received a 5-month course of aspirin (1.6 g/d until steroid withdrawal and then 0.8 g/d). During follow-up (mean, 42 months), high-dose prednisone resulted in stable remission in all but 1 patient. Prolonged treatment with aspirin cannot be excluded to explain the overall good remission rate. Moreover, 3 patients (25%) had severe steroid-related adverse effects; 2 were treated with other immunosuppressive treatments (1 with azathioprine and 1 with cyclophosphamide).

A recent retrospective, nonrandomized study challenges the common practice of using these high doses of corticosteroids.<sup>9</sup> One hundred patients with recurrent pericarditis were assigned to 2 alternative therapeutic regimens of prednisone; one half received “low” doses of prednisone (0.2 to 0.5 mg/kg/d), and the other half received prednisone 1.0 mg/kg/d. Each initial dose was maintained for 4 weeks and then slowly tapered. During 5580 patient-months of follow-up, patients treated with high doses of prednisone had not only a higher rate of severe side effects (23.5% versus 2.0%) but also of recurrences (64.7% versus 32.6%) and disease-related hospitalizations (31.4% versus 8.2%). On this basis, a premise for a possible future randomized study, low doses of corticosteroids may be considered before resorting to higher doses.

A very low tapering only after stable remission with symptom resolution and normalization of CRP is the key to successful management of the disease. A critical threshold for recurrences is a 10- to 15-mg/d dose of prednisone; at this threshold, very slow decrements as small as 1.0 to 2.5 mg at intervals of 2 to 6 weeks are useful (Table V). If symptoms recur during tapering, every effort should be made not to increase the dose of or to reinstitute corticosteroids and to control symptoms by beginning or increasing the doses of aspirin or NSAIDs. During tapering, colchicine should always

**Table V. Medical Therapy for Pericarditis and Tapering Regimen of Prednisone in Pericarditis**

Drug	Usual Attack Dose* (Dose Range)	Time for Attack Dose†	Tapering (Every 1-2 wk)‡
Acetylsalicylic acid	750-1000 mg TID (2-4 g/d)	First attack: 1-2 wk Recurrence: 2-4 wk	750-1000 mg BID and then 750-1000 mg/d
Ibuprofen	600 mg TID (1600-3200 mg)	First attack: 1-2 wk Recurrence: 2-4 wk	600 mg BID or 400 mg TID and then 600 mg/d
Indomethacin	50 mg TID (75-150 mg)	First attack: 1-2 wk	75-150 mg/d (ie, TID but reduce the daily dose of 25 mg every 1-2 wk)
Nimesulide	200 mg/d	First attack: 1-2 wk Recurrence: 2-4 wk	100-200 mg/d
Prednisone	0.2-0.5 mg./kg <sup>1</sup> .d <sup>1</sup>	First attack: 2 wk Recurrence: 2-4 wk	>50 mg: 10 mg/d every 1-2 wk 50-25 mg: 5-10 mg/d every 1-2 wk 25-15 mg: 2.5 mg/day every 2-4 wk <15 mg: 1.0-2.5 mg/day every 2-6 wk
Colchicine	0.5 mg BID 0.5 mg/d (<70 kg)‡	First attack: 3 mo Recurrence: 6-12 mo	Optional for worse recurrent cases; consider tapering over 2-4 wk

Very slow tapering is recommended especially in recurrent cases. Osteoporosis prevention should follow guidelines. Higher doses of corticosteroids are not proven to improve the outcome in unselected recurrences but may increase the risk of side effects, further recurrences, and hospitalization.

\* Proton-pump inhibitors are recommended for aspirin and NSAIDs.

† Every decrease in drug dose should be only done if the patient is asymptomatic and CRP and/or ESR are normal, usually after 1 to 2 weeks or longer for corticosteroids with prednisone <25 mg/d or equivalent. Minimal monitoring for antiinflammatory drugs includes blood cell count and CRP at baseline and weekly until CRP normalizes; for colchicine, consider blood cell count, CRP, transaminases, creatine kinase, and creatinine at baseline and at least after 1 month.

‡ For colchicine, an attack dose is not necessary (risk of increased rate of side effects; use the maintenance dose); 0.5 to 0.6 mg/d is the maximum dose for children <5 years of age and elderly >70 years of age. For renal impairment, use 0.5 to 0.6 mg/d if creatinine clearance is 35 to 50 mL/min and 0.5 to 0.6 mg/d every 2 to 3 days if creatinine clearance is 10 to 34 mL/min; it should be avoided if creatinine clearance is <10 mL/min.

be considered, starting with low doses, eg, 0.5 to 0.6 mg, to improve gastrointestinal tolerability.

The toxic effects of oral steroid administration are significantly lessened by injecting a nonabsorbable preparation intrapericardially, as was recommended for pericardial effusion in patients with late-stage renal disease. Intrapericardial administration of triamcinolone is, by the same token, a good option for recurrent pericarditis and has the added advantage that the steroid is delivered where it contacts the 2 pericardial surfaces. However, the technique still remains investigational.

#### NSAIDs and Aspirin

Aspirin or NSAIDs remain the mainstay of treatment for pericarditis (Table V). Unsatisfactory results are often reported when NSAIDs are used. Some of these failures are due to low dosages or courses that are too short, with interruption of the therapy while the disease is still active,

as manifested by persistently elevated CRP. NSAIDs should be used at appropriate antiinflammatory dosages (eg, aspirin at 2 to 4 g daily, indomethacin at 75 to 150 mg daily, and ibuprofen at 1600 to 3200 mg daily), considering long courses until complete normalization of CRP (Table V). This is particularly important during corticosteroid tapering. The selection of the specific NSAID should be based on physician experience and the patient's previous history (eg, an NSAID that was effective in previous attacks should be the favorite choice) and comorbidities; eg, aspirin is the favored choice in patients with ischemic heart disease or when the patient is already on aspirin or needs antiplatelet treatment, whereas indomethacin and other NSAIDs should be avoided in patients with coronary artery diseases.

The optimal length of treatment is debatable, and CRP should probably be considered as a marker of disease activity to guide management and treatment length. In addition, the

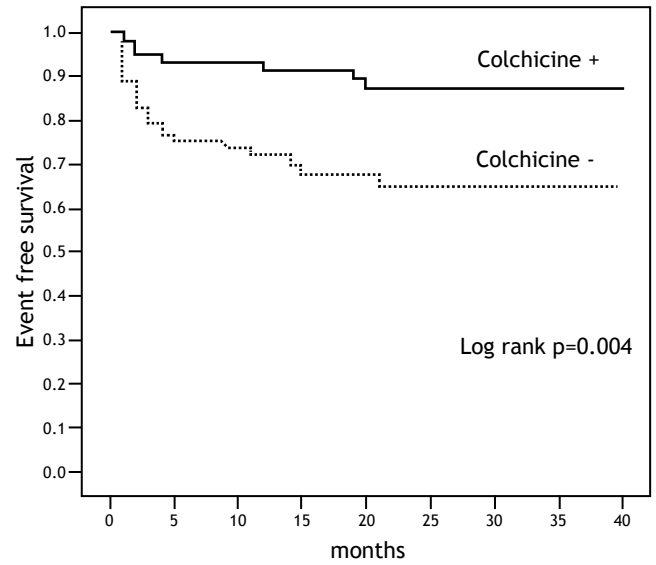
need for gradual tapering is not well established although often proposed in recent publications on pericarditis management.

**Colchicine**

Besides the indication for gout, colchicine is effective for treating serositis in familial Mediterranean fever. Following this successful use, Rodriguez de la Serna first proposed colchicine for recurrent pericarditis in 1987.

A number of small retrospective studies support the use of colchicine for recurrent cases (Table VI); in addition, in a retrospective multicenter analysis of 119 patients, corticosteroids attenuated the efficacy of colchicine in preventing recurrent pericarditis. On this basis, more for expert consensus than randomized clinical trials, colchicine has been recommended to treat recurrent pericarditis (class I recommendation) and is considered optional but probably useful in acute pericarditis (class IIa recommendation) in the 2004 European guidelines. The guidelines recommend 2 mg/d for 1 to 2 days, followed by a maintenance dose of 1 mg/d.

The stronger evidence base to support the use of the drug, above all for primary or secondary prevention of recurrences, comes from the subsequent first 2 open-label randomized trials in which colchicine at least halved the recurrence rate.<sup>10-11</sup> In the Colchicine for Pericarditis (COPE) trial (Figure 1), Colchicine (0.5 to 1 mg daily for 3 months) as an adjunct to conventional treatment significantly decreased the recurrence rate (actuarial rates at 18 months were 10.7% and 32.3%, respectively; P=0.004; number needed to treat, 5.0) and symptom persistence at 72 hours (11.7% and 36.7%; P=0.003) in 120 patients with a first episode of acute pericarditis. In this study, colchicine was discontinued in 5 patients (8.3%) because of diarrhea.



Patients at risk

Colchicine+	60	58	52	45	39	33	14	
6Colchicine-	60	45	44	32	24	18	11	7

**Fig. 1: Kaplan-Meier event-free survival curves for patients with and without colchicine in COPE trial. Improved event free survival in the group receiving Colchicine**

In the Colchicine for Recurrent Pericarditis (CORE) trial, colchicine (0.5 to 1 mg daily for 6 months) as an adjunct to conventional treatment for recurrent pericarditis significantly decreased the recurrence rate (actuarial rates at 18 months, 24.0% versus 50.6%, respectively; P=0.022; number needed to treat, 4.0) and symptom persistence at 72 hours (9.5% versus 31.0%, respectively; P=0.029) in 84 patients with recurrent pericarditis. In both CORE and COPE, a maintenance dose of 0.5 mg BID was adopted and reduced to 0.5 mg daily in patients <70 kg; thus, lower doses may

**Table VI. Main Published Studies on the Use of Colchicine to Treat Recurrent Pericarditis**

Study	Year	Design	Patients, n	Maintenance Dose, mg/d	Adjunct to Standard Therapy	Follow-Up, mo	Recurrence, n (%)
Guindo et al	1990	NR	9	1.0	Yes	10-54	0/9 (0.0)
Adler et al	1994	NR	8	1.0	Yes	18-34	0/8 (0.0)
Millaire et al	1994	NR	19	1.0	No	32-44	4/19 (21.0)
Adler et al	1998	NR	51	1.0	Yes	6-128	7/51 (13.7)
Imazio et al	2005	NR	35	1.0	Yes	48-108	3/35 (8.6)
CORE	2005	R	84	0.5-1.0	Yes	8-44	9/42 (21.0)

NR indicates nonrandomized; R, randomized.

be equally efficacious but with a possible lower rate of side effects. Treatment was for 3 months in the first episode (COPE) and 6 months in recurrent pericarditis (CORE).<sup>(45,46)</sup> In recurrent more severe cases, some authors advocate a longer use of the drug: up to 12 to 24 months after the last recurrence, tailored to the individual patient and with gradual tapering, considering that recurrences have been described after colchicine discontinuation.

Clinicians are often skeptical about the possible utility of colchicine for pericarditis. Common reasons include further recurrences on treatment (colchicine halves, but does not erase all recurrences); failure as monotherapy (efficacy has been demonstrated almost exclusively for combination therapy with an NSAID or corticosteroid); incorrect use in chronic pericardial effusions with normal CRP, a condition in which colchicine is generally not efficacious; and drug withdrawal because of gastrointestinal intolerance. Practical tips to improve drug compliance may be using appropriate weight-adjusted doses and starting with lower doses without a loading dose and then increasing the dose if tolerated. Compared with other drug treatments, colchicine appears to be one of the cheapest therapy.

#### Management of “Refractory” Cases

Cases that recur after steroid tapering (very common) should not be considered refractory; this definition should apply to those cases that require unacceptably high long-term doses of corticosteroids to be controlled (eg, prednisone >25 mg daily). They probably represent <5% of recurrent cases. In this situation, several drugs (azathioprine, cyclophosphamide, cyclosporine, methotrexate, hydroxychloroquine, intravenous immunoglobulin, anakinra) have been used; azathioprine is the preferred choice if tolerated (at the common dosage of 2 to 3 mg/kg/d), but it should be acknowledged that strong evidence-based data are lacking. Less toxic and less expensive drugs (eg, azathioprine or methotrexate) should be preferred, with the therapy tailored to the individual patient and physician experience and, importantly, with informed consent. In many cases, combined triple therapy with a corticosteroid, aspirin or an NSAID, plus colchicine may be considered in more difficult cases.

#### Restriction of physical activity

The role of physical activity in the recurrence and exacerbation of pericarditis is unknown. However, in clinical practice it is not uncommon that some patients report a worsening of symptoms apparently provoked

by exercise. This is especially frequent in patients with persistent precordial pain as the only manifestation of their illness, while the role of exercise as a trigger of evident inflammatory relapses (fever, pericardial friction rub, pericardial effusion) is much less clear. In any case, it seems reasonable to restrict physical activity, particularly when the patient is weaned from prednisone or other anti-inflammatory drugs. The desirable amount of restriction cannot be known in the absence of appropriately designed controlled trials, but it is advisable to restrict exertion beyond what is necessary to perform domestic tasks and undertake sedentary work.

#### Role of Pericardiectomy, Pericardial Window, and Other Interventional Techniques

The 2004 European Society of Cardiology guidelines<sup>12</sup> gave a class IIa recommendation to pericardiectomy for frequent and highly symptomatic recurrences resistant to medical treatment. Other reported indications include repeated recurrences with cardiac tamponade, as well as evidence of serious steroid toxicity. Although surgical experiences are not always concordant, pericardiectomy is generally considered a therapeutic option of doubtful efficacy in recurrent idiopathic pericarditis and should be considered only in exceptional cases.

There have been cases in which, for unknown reasons, pericardial removal has ended the syndrome, but there are also many cases in which the syndrome either is unchanged or returns postoperatively after a period of improvement or even disappearance. This frequent “lucent period” may last from as little as 9 days to 6 months and is probably responsible for early reports of successful surgery (ie, the follow-up was inadequate).

Less invasive options for recurrent symptomatic effusions are derived mainly from experience in the management of neoplastic pericardial effusions and include prolonged catheter drainage and the creation of the so-called “pericardial window.” Prolonged catheter drainage is an effective means of preventing fluid reaccumulation, although the mechanism by which this occurs is probably related more to the obliteration of the pericardial space after inflammation provoked by the catheter than to fluid drainage itself. This approach was successful in >70% of cases, although the duration of effusion control is often not reported. Catheter drainage may be required for several days, and the catheter should not be removed until drainage is <20 to 30 mL/24h. Alternative strategies



include surgical decompression of the pericardium (also known as pericardiotomy, pericardiostomy, and “window” pericardiectomy) by either conventional heart surgery or video-assisted thoracoscopy with a possible lower incidence of effusion recurrence compared with pericardiocentesis and prolonged catheter drainage.

Balloon pericardiectomy is an alternative to surgical creation of a pericardial window. The technique has been especially adopted for patients with malignancies and reduced life expectancy to improve the quality of life. It involves inserting a deflated single catheter or double balloon catheters into the pericardial space using a subxiphoid approach under fluoroscopic guidance. Although successful in preventing recurrence in >80% of cases, stretching of the pericardium is often painful, so appropriate analgesia is recommended. Reported complications include fever (up to 28%), pneumothorax or need for a chest tube (up to 20%), and rarely bleeding from a pericardial blood vessel.

#### FUTURE

Worthwhile progress has been made in the treatment of acute and recurrent pericarditis, but in recurrent pericarditis many issues require investigation. We need to find reliable noninvasive methods that will distinguish autoimmune cases from those caused by reinfection or new infection, and trials of treatment based on cause. If we can learn how to predict the outcome of pericardiectomy, then that would be a notable advance. The riddle of recurrent pain without evident pericarditis remains to be solved, and therefore the place in it for anti-inflammatory treatment is

uncertain. The exact mechanism of the action of colchicines in recurrent pericarditis is in need of clarification. We lack an animal model of recurrent pericarditis. Research will include basic and clinical immunology as well as virology and a search for still more effective drugs.

#### CONCLUSION

The most frequent causes of relapsing pericarditis are idiopathic or viral pericarditis and post pericardial injury syndromes. In patients without previous cardiac surgery, and in whom connective tissue disease has been ruled out, relapsing-intermittent pericarditis with symptom-free periods longer than six weeks makes the diagnosis of idiopathic/viral pericarditis practically certain. The clinical evolution is characterised by the recurrence of the episodes of acute pericarditis, which frequently are progressively less severe, without clinical tamponade, and without evolution to constrictive pericarditis. Fortunately, only few cases develop the incessant type of relapsing pericarditis. The treatment modalities include anti-inflammatory therapy - Cortico steroids, NSAIDS, Aspirin, Colchicine & immunosuppressives (Refractory cases). Interventional techniques like pericardiectomy, pericardial window and intra pericardial administration of triamcinolone have limited role.

Successful management requires a lot of patience on the part of physicians and patients. Patients must be informed about what is known about the condition and the merits and problems associated with the various therapeutic options, including pericardiectomy.

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