

## Recurrent pericarditis

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### CLINICAL REVIEW

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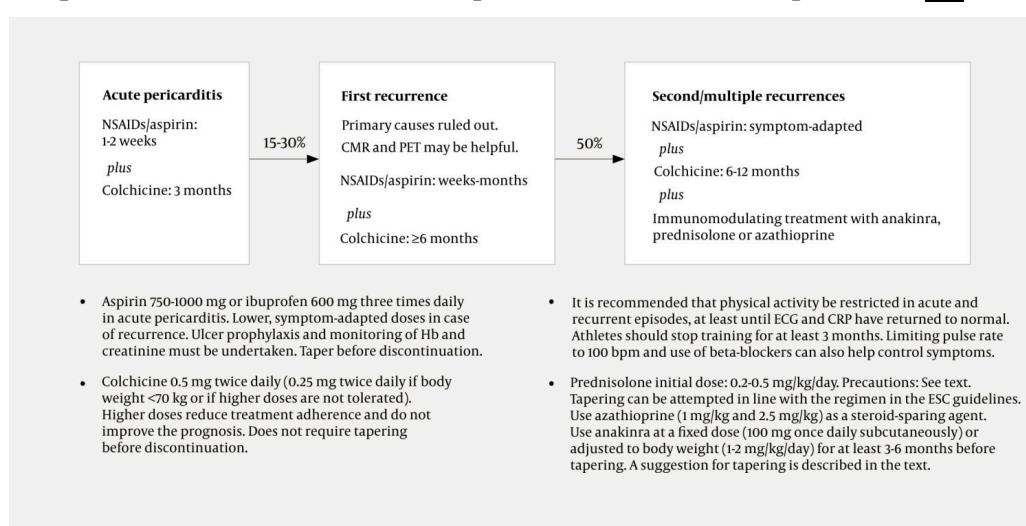
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**Pericarditis is an important differential diagnosis in patients with chest pain. The two most common causes in the developed world are idiopathic pericarditis and inflammation following cardiac surgery or myocardial infarction. Recurrence of pericarditis affects up to 30 % of patients, half of whom experience multiple episodes, and approximately 10 % develop steroid-dependent and colchicine-refractory pericarditis. Recurrence is due to autoinflammatory processes in the pericardium. Advanced diagnostic imaging and treatment with colchicine and interleukin-1 inhibitors has helped reduce morbidity considerably in recent years. In this clinical review, we summarise up-to-date knowledge about the diagnostic evaluation and treatment of patients with recurrent primary pericarditis.**

Pericarditis may be the cause in 5 % of patients presenting to the emergency department with chest pain (1). With rapid initiation of the correct treatment, the prognosis for acute pericarditis is good. However, recurrence affects up to 30 % of patients and causes considerable morbidity (Figure 1) (2, 3). Half of patients who experience recurrence have multiple episodes, and up to 10 % develop steroid-dependent and colchicine-refractory pericarditis (3, 4). Risk factors for recurrence are younger age, female sex, fever, tachycardia above 120 bpm, low platelet count, signs of constriction on echocardiography, use of prednisolone and treatment that does not include colchicine (5, 6). Cardiac tamponade and calcific constrictive pericarditis are rare complications (3).



**Figure 1** Overview of treatment for primary pericarditis according to the European Society of Cardiology (1).

New knowledge about the autoinflammatory disease process that causes the recurrences, about diagnostic imaging and about medication has changed the treatment of recurrent pericarditis. In this clinical review, we summarise new knowledge about the pathogenesis, diagnostic evaluation and treatment of patients with recurrent primary pericarditis. The article is based on a literature search in PubMed, publications from relevant specialist associations and research groups, and the authors' clinical experience.

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## Pathogenesis

The causes of pericarditis are classified into three main groups: non-infectious inflammation, drug-induced pericarditis and infections. All groups present the same pattern of inflammation in the pericardium (7). Idiopathic pericarditis that has no known underlying cause is the most common type in the developed world (1). Some of these cases may develop as a result of a viral infection, but diagnostic evaluation to differentiate between idiopathic and viral causes is not routinely recommended (1). Pericarditis also occurs following myocardial infarction, open and percutaneous cardiac surgery, and trauma (3). Metabolic disease, tuberculosis, other infections, cancer and rheumatological disease are rare causes in Norway. Furthermore, pericarditis is an uncommon primary manifestation of these diseases (7). Globally, tuberculosis is still a common cause of pericarditis and an important differential diagnosis because curative treatment is available.

At a molecular level, release of interleukin-1 $\beta$  and interleukin-18 is central in the pathogenesis of pericarditis (8) and takes place primarily from inflammasomes in macrophages. In recurrent pericarditis, release occurs independently of the original cause, which is a typical feature of autoinflammation (9). Therefore, the condition is also known as recurrent autoinflammatory pericarditis (9).

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## Diagnostic evaluation

Acute pericarditis is diagnosed in line with the criteria of the European Society of Cardiology (ESC), and at least two of the following four criteria must be fulfilled (1): 1) Typical chest pain that varies with breathing and position. This is the most common symptom and is present in up to 80 % of patients. The pain often radiates to the superior portion of the trapezius muscle, but can also imitate ischaemic chest pain. 2) ECG changes in the acute phase, typically diffuse concave ST-segment elevation without coronary artery distribution. This can disappear and be followed by T-wave inversion before ECG normalisation. 3) Pericardial effusion on imaging investigations. As with ECG changes, this occurs in around half of patients. 4) Pericardial friction rub. This can be hard to hear in a busy emergency department, and there are considerable differences in the frequency reported in the literature.

Inflammatory markers, such as erythrocyte sedimentation rate or CRP, are elevated in most patients, but are not included in the diagnostic criteria. Onset without typical chest pain in younger patients and in cases of secondary pericarditis, but also lack of awareness about the symptoms, contribute to probable underdiagnosis of pericarditis (3).

Before diagnosing recurrent pericarditis (Box 1), it is important to rule out primary causes of recurrence, for example tuberculosis, rheumatological diseases and cancer (7). The objective findings are often less pronounced in recurrent pericarditis, and only 50 % fulfil the ESC criteria for acute pericarditis. Therefore, multimodal diagnostic imaging and inflammatory markers, such as erythrocyte sedimentation rate and CRP, are highly significant in the diagnostic evaluation (1, 3). CRP is elevated in 70–80 % of patients with recurrent pericarditis. Specific diagnostic criteria for recurrence have also been proposed (7), but these are rarely used in clinical practice.

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#### **Box 1 Definition of complicated pericarditis according to the European Society of Cardiology (ESC) (1).**

Complicated pericarditis is classified into three groups according to the ESC definition:

##### **Subacute pericarditis**

Lasting longer than four to six weeks, but shorter than three months.

##### **Chronic pericarditis**

Lasting longer than three months.

##### **Recurrent pericarditis**

A new episode after documented acute pericarditis and a symptom-free interval of least four weeks.

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Low-level troponin release ('myo-pericarditis') is generally of little prognostic value (8) but may be an indication for performing either echocardiography or cardiac magnetic resonance (CMR) to distinguish between *myo-pericarditis* and *peri-myocarditis*, in cases where the myocarditis component is predominant and different workup and treatment are needed. Analysis of NT-proBNP should also take place in cases of recurrence. Significantly elevated levels of ferritin (as a sign of macrophage activation) and soluble interleukin-2 receptor (sign of T-cell activation) indicate a complicated disease progression with more pronounced immune activation. Non-specific mildly elevated levels of antinuclear antibodies and other autoantibodies are seen often, but are of little significance for the disease process.

Echocardiography is the most accessible diagnostic imaging method and should be performed before initiating treatment and in the event of any recurrence to evaluate possible tamponade and pericardial constriction (1). Pericardial effusion is found in approximately 40 % of patients with recurrence (10). Signs

of pericardial constriction are detected more frequently in cases of recurrence, particularly with a subacute course (10, 11). Constriction can often be transient with appropriate anti-inflammatory treatment (12).

The indication for CMR in pericarditis has been bolstered in recent years (8, 13). CMR can provide information about the extent of inflammation, myocardial involvement, pericardial thickness, amount of pericardial effusion, haemodynamics and prognosis (8). CMR can also be used to guide treatment (13). There is less evidence for the use of CT and PET, but both can be important investigations if extra-cardiac systemic manifestations are suspected (1). PET can also detect active pericarditis in individual cases in which diagnosis cannot easily be made with CMR (14).

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## Treatment

Acute primary pericarditis and recurrence are treated with a combination of non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin and colchicine (Figure 1) (1). Restriction of physical activity is recommended (1). Colchicine as an adjunct to NSAIDs or aspirin produces more rapid resolution of symptoms and reduced risk of repeat hospitalisation and recurrence (1). Colchicine as maintenance treatment can also prevent recurrence in some patients.

In cases of acute primary pericarditis or a first recurrence, corticosteroids should only be used in patients with a contraindication for colchicine and NSAIDs or aspirin (1). The ESC guidelines recommend the use of corticosteroids such as prednisolone for subsequent recurrences (1). Tapering should take place over several months and only when the patient remains in remission during tapering (1). Nevertheless, many patients experience recurrence when the prednisolone dose is tapered to 10–15 mg daily (4). Long-term use of corticosteroids often leads to serious adverse reactions. Therefore, HbA1c, lipid profile, blood pressure and bone density must be measured, and prophylactic treatment given to prevent gastric ulcer and osteoporosis. Corticosteroids have also been associated with a dose-related risk of recurrence (5, 6). In the event of recurrence during tapering, consideration should be given to initiating treatment with immunomodulating drugs such as anakinra, azathioprine or intravenous immunoglobulins (IVIG) (1).

Following new understanding about the pathogenesis, there is increasing evidence for the use of interleukin-1 inhibitors in the treatment of recurrent pericarditis (15). The most widely used drug is anakinra (interleukin-1 receptor antagonist) as a daily subcutaneous injection (16). Anakinra has a half-life of approximately four to six hours, and in certain serious cases it may be appropriate to give a full dose two to three times daily at treatment initiation. When concomitant treatment is administered with prednisolone, NSAIDs or aspirin and colchicine, these can be tapered, one at a time, once the patient is in remission (1). Monotherapy with anakinra is adequate for most patients after eight to ten weeks (16). An attempt to taper anakinra can be made after three to six months, for example with the reduction of one daily dose per week every two or three weeks over a period of at least three months (16). Consideration

can be given to attempting discontinuation, but the duration of treatment and tapering may have an impact on the rate of recurrence (16). Recurrence is experienced by 33–71 % of patients after tapering, and consequently anakinra (one to three injections per week) often needs to be administered for several years (4).

Use of interleukin-1 inhibitors early in the disease course and before initiating treatment with corticosteroids can be considered if there are signs of pericardial constriction, widespread inflammation on CMR, subacute course and high levels of CRP, ferritin or soluble interleukin-2 receptor (11, 16). Remission is usually achieved after a few days of treatment with anakinra. A lack of response should lead to further workup to investigate differential diagnoses. Transient cutaneous reactions at the injection site are common, while other adverse reactions, such as impact on liver function tests and leukopenia, are rare (16). It is important that the patient is trained in the use of anakinra and properly informed about the management of adverse reactions to prevent early discontinuation of treatment.

In the event of adverse reactions with anakinra, canakinumab, an anti-interleukin-1 $\beta$  antibody, can be tried. However, making such a switch requires that anakinra has been effective since canakinumab has the same mechanism of action (17). Canakinumab is administered every four to eight weeks and causes considerably fewer cutaneous reactions than anakinra, although the price is much higher.

Before initiating treatment with interleukin-1 inhibitors, pregnancy, tuberculosis, HIV and hepatitis B and C must be ruled out. Liver function tests and blood count must be checked before the start of treatment and after one month (16), and thereafter every three months during administration of the drug. Vaccination status should be updated before starting treatment, although patients can receive all non-live vaccines during treatment.

Azathioprine and intravenous immunoglobulins are possible alternatives to anakinra in cases of recurrent pericarditis, although the evidence for treatment with these drugs is sparse. Interleukin-6 inhibition, for example with tocilizumab, can be considered in the event of an incomplete response to anakinra with considerable elevation of CRP and interleukin-6 levels. However, there is little evidence for treatment with interleukin-6 inhibitors, and only for pericarditis associated with rheumatic diseases (18).

Pericardectomy may be appropriate for individual patients with irreversible pericardial constriction when laboratory tests and imaging investigations no longer show signs of inflammation (19). Before pericardectomy is considered, simultaneous right and left heart catheterisation should be performed to evaluate haemodynamic impact. Pericardectomy is advanced surgery, but has potentially very good results at highly specialised centres (19).

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## Follow-up

In our opinion, investigation and treatment of acute pericarditis and recurrent pericarditis should take place at hospitals with expertise in cardiology. Initially, patients with pericarditis should receive close follow-up, depending on their clinical condition, for example after two to four weeks, and subsequently after six to eight weeks. However, once remission is achieved, the intervals can be extended and the general practitioner may be involved.

Clinical assessment and CRP can be used for follow-up (1). Repeat echocardiography or CMR are indicated if there are signs of heart failure, if the patient deteriorates with no change in therapy or does not achieve remission despite treatment in line with the guidelines. Patients with signs of constriction on echocardiography or CMR must also receive close follow-up, for example with echocardiography after one and three months, and thereafter every six months (11).

Rheumatology assessment may be helpful if there are signs of extensive inflammation or subsequent recurrences. Rheumatology follow-up may be advisable if immunomodulating treatment is administered. Contact with rheumatology nurses is also helpful for patients to obtain answers to questions about how to deal with, for example, adverse reactions, vaccinations and infections.

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## Conclusion

Patients with recurrent pericarditis are treated by doctors in a wide range of specialties, such as emergency medicine, general medicine, cardiology and rheumatology. It is important to consider the disease as a possible differential diagnosis in patients with chest pain. Multimodal imaging increases diagnostic certainty, and novel treatments with interleukin-1 inhibitors can help to lower morbidity considerably.

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