

ACUTE PERICARDITIS

Definitions

Pericarditis indicates inflammation of the pericardium due to various causes. Acute pericarditis refers to an event lasting <4 to 6 weeks.¹⁻³ **Inflammatory myopericardial syndrome (IMPS)** is an umbrella term to increase understanding of the potential myocarditis–pericarditis overlap (See Chapter on Myocarditis).⁴

Epidemiology

Exact data are lacking. The incidence has been reported as 27.7 cases per 100,000 person-years.¹ Pericarditis is diagnosed in 0.2% of hospitalized patients, and in 5% of patients seen in the emergency room with chest pain but without myocardial infarction.¹⁻³

Aetiology

Causes and estimated incidence of acute pericarditis are presented in Table 1. In 80-90% of patients the cause is either viral or unknown (idiopathic). **Idiopathic** pericarditis is thought to be very common because the yield of diagnostic tests to confirm etiology is relatively low. The major specific causes to be ruled out are causes are **tuberculous pericarditis, metastatic neoplasia, and connective tissue disorders**.⁵ Indicators of non-viral aetiologies are presented in Table 2. Pericarditis may be a marker of occult **cancer** such as lung and bladder cancer, non-Hodgkins lymphoma and myeloid leukemia, and indicates increased mortality following a cancer diagnosis.^{6,7} **Tuberculous** pericarditis in high-income countries, accounts for up to 4% of pericardial disease, but it is increasing due to immigration. However, it is the cause of clinically significant pericardial effusion in approximately 90% of HIV-infected and 50%–70% of non-HIV-infected individuals living in developing countries with a high prevalence of tuberculosis.⁴ The term **post-cardiac injury syndrome** is an umbrella term indicating a group of inflammatory pericardial syndromes, including late post-acute myocardial infarction pericarditis (or Dressler syndrome), postpericardiotomy syndrome, and post-traumatic pericarditis with or without bleeding.⁴

Presentation

Fever, myalgia and malaise may occur as a prodromal phase (Table 3). Body temperature >38°C is uncommon and may indicate purulent pericarditis.

Chest pain is usually sudden in onset, retrosternal, typically accentuate by inspiration and attenuated by leaning forward. Radiation of the pain to trapezius muscle ridges is

probably due to pericarditis because the phrenic nerve that innervates these muscles traverses the pericardium.⁸ Dull pain imitating myocardial ischemia may also occur.

Pericardial friction rub is a high-pitched, scratchy sound heard at the left sternal border. It is present in up to 85% of patients but may be transient (repeat examinations are required), and mono-, bi- or tri-phasic (corresponding to atrial systole, ventricular systole, and rapid ventricular filling). It is audible throughout the respiratory cycle, whereas a pleural rub is absent when respiration is suspended.

Investigations

Diagnostic criteria for pericarditis are:

- Typical chest pain
- Pericardial friction rub
- Suggestive ECG changes (typically widespread ST-segment elevation, PR depression)
- New or worsening pericardial effusion (not necessary)
- Elevated CRP (not specific)

ECG. Four stages have been described (Figure 1):

- *Stage 1:* Diffuse ST-segment elevation (epicardial inflammation) and PR-segment depression with reciprocal ST-segment depression in the aVR and V1 leads, within the first hours to days (present in 80% of patients with pericarditis). There can also be PR-segment elevation in the aVR (atrial injury).
- *Stage 2:* The ST and PR segments normalize.
- *Stage 3:* T-wave inversions.
- *Stage 4:* ECG normal or T-wave inversions persist indefinitely.

Differential diagnosis from myocardial infarction:

In STEMI:

- ST-segment elevations are often convex rather than concave, and regional rather than widespread
- T-wave inversions appear before the ST segments return to baseline
- Q-wave formation and loss of R-wave voltage often occur
- PR segment depression is uncommon
- Atrioventricular block or ventricular arrhythmias may be seen.

A ratio of the height of the ST segment junction to the height of the apex of the T wave of more than 0.25 in lead V₆ is suggestive of pericarditis (Figure 2).^{9, 10}

Chest X-ray shows cardiomegaly only with effusions > 250 ml.

Echocardiography may be normal or show a small effusion. A paediatric transoesophageal echo probe inserted into a chest drain in the pericardial space allows rapid assessment of postoperative effusions.¹⁰

Cardiac CT and CMR provide excellent visualization of the pericardium and pericardial space. Normal pericardial thickness is usually 1-2 mm (< 4 mm). Delayed gadolinium enhancement on CMR is expected to be increased during active inflammation (increased pericardial neovascularization), and represents the most sensitive method for diagnosis of acute pericarditis.⁸ It is particularly helpful when the diagnosis is uncertain, echocardiographic imaging is challenging, or myocardial involvement is suspected (Table 4).

Troponin concentrations are elevated in 30-50% of cases (CK-MB less often) due to epicardial inflammation. Persistence more than two weeks suggests myocarditis. Unlike acute coronary syndromes, troponin elevation is not a negative prognostic marker in myopericardial inflammatory syndromes. Myopericardial inflammatory syndromes (myopericarditis/perimyocarditis) are rather benign clinical syndromes that can be frequently encountered in patients with an initial suspicion of pericarditis.¹¹

Viral cultures and **antibody** testing are not useful clinically, with possible exception of HIV and HCV.¹²

WBC, ESR and CRP are usually elevated. Marked WBC elevation may suggest purulent pericarditis.

Antinuclear antibody and **rheumatoid factor**, **tuberculin skin test** or **QuantiFERON-TB assay**, and **HIV** testing should be ordered only if the clinical presentation is suggestive of these diseases.

Pericardiocentesis is indicated in tamponade or if purulent, tuberculous, or neoplastic pericarditis is suspected.³ Patients with pericarditis and pericardial effusion should be investigated for occult cancer.⁶ Pericardial fluid is analyzed for cell count, microscopy (including gram and Ziehl-Nielsen stain), bacterial culture, and cytological examination. PCR techniques can identify causative viruses and *M tuberculosis*. Immunohistochemistry techniques can identify antibodies to myolemma and sarcolemma in immune-mediated pericarditis.¹⁰ Concentrations of adenosine deaminase activity > 30 U/L in pericardial fluid are specific for *M tuberculosis* and can predict constriction. Carcinoembryonic antigen concentrations are higher (5 ng/mL) in neoplastic than in benign effusions. Measurements of pH, glucose, protein, and lactic dehydrogenase are also routinely done but no accepted criteria link such measures to specific causes of pericarditis.⁹ A gold paint characteristic suggests the rare diagnosis of *cholesterol pericarditis* than can very rarely be seen in myxedema, rheumatoid arthritis, tuberculosis, and viral infections although most cases are considered idiopathic.¹³

Pericardial biopsy should be considered for patients who have recurrent tamponade despite

treatment. In subjects with tamponade of unknown cause, pericardiocentesis and pericardial biopsy provided a diagnosis in 29% and 54% of cases, respectively.⁹

A diagnostic flowchart in some common conditions in high risk patients is presented in Figure 3 and Table 5.

Therapy

When the aetiology is identified, therapy is directed towards treating the underlying cause. Patients with idiopathic pericarditis and without predictors of poor prognosis can be managed as outpatients.¹²

Predictors of poor prognosis are:

Major: Fever $>38^{\circ}\text{C}$, subacute onset, large effusion, tamponade, lack of response to aspirin or NSAID after 1 week.

Minor: immunosuppression, trauma, oral anticoagulation.

Aspirin (750-1000 mg tds for 7 days, with 500 mg tds for 1 additional week) or a NSAID such as **ibuprofen** (600-800 mg tds for 7 days, followed by 200-400 mg tds for another week), or **naproxen** (500-1000 mg bd) with gastroprotection usually with proton pump inhibitors, are preferred (Tables 6 and 7, and Figure 4). **Colchicine** (1.0 to 2.0 mg for the first day and then 0.5 mg od (patients weighing $<70\text{ Kg}$) or bd (patients weighing $>70\text{ Kg}$) for 3 months with tapering not mandatory) is now considered a first-line therapy as an adjunct to aspirin or NSAIDs, reducing the recurrence rate by 50%, as well as the risk of tamponade or constriction.¹⁴ It should be noted, however, that in patients with concomitant myocarditis there is lack of clinical evidence regarding its safety.¹ In the recent ICAP trial, in patients with acute pericarditis, colchicine, when added to conventional anti-inflammatory therapy, significantly reduced the rate of incessant or recurrent pericarditis.¹⁵ It is generally well tolerated during long-term administration, and most common side-effect are diarrhea, nausea and vomiting ($<10\%$). Reversible alopecia, hepatic or bone marrow toxicity are very rare. It is avoided in patients with severe renal insufficiency, hepatobiliary dysfunction, blood dyscrasias, and gastrointestinal motility disorders.⁸ Reduced dosage is recommended for patients $< 70\text{ kg}$, or with advanced renal dysfunction or concurrent therapy with moderate to strong inhibitors of CYP3A4 (eg, protease inhibitors, ketoconazole, fluconazole, erythromycin, diltiazem, verapamil) or P-glycoprotein inhibitors (eg, cyclosporine). In patients undergoing cardiac surgery, perioperative use of colchicine reduces the incidence of postpericardiotomy syndrome but not of postoperative AF (but there was a reduction in postoperative AF in the prespecified on-treatment analysis) or postoperative pericardial/pleural effusion.¹⁶ **Corticosteroids** increase the risk of relapsing pericarditis and should be used, together with colchicine, only if aspirin/NSAID are contraindicated.¹

Prednisone (0.25-0.5 mg/kg/day with gradual tapering by 20% of the dose every 1-2 weeks) is given for 4 weeks. As initial treatment steroids may be used only when the underlying cause is an immune-mediated disease, a connective tissue disorder, or uremic pericarditis. Despite promising initial indications, they do not seem to reduce the incidence of constriction in tuberculous pericarditis.¹⁷ Novel therapies include ***anakrina*** (an interleukin-1 receptor antagonist), ***azathioprine***, ***mycophenolate mofetil***, and ***human intravenous immunoglobulin***.^{1, 18}

The management of pericardial diseases in patients receiving ***cancer*** therapy is presented in Table 8, for ***post-cardiac injury syndrome*** in Table 9 and for purulent pericarditis is Table 10. Tuberculous pericarditis is discussed in Figure 5 and Table 11.

After discharge, patients, and especially female, exhibit higher rates of morbidity, cardiovascular and noncardiovascular hospital readmissions, and mortality over 5 years than matched control individuals.¹⁹

Exercise restriction recommendations are provided in Table 12.^{20, 21}

In ***pregnancy***, NSAIDs may be considered during the first and second trimesters, but high-dose aspirin may be preferable, since it is regularly used in antiphospholipid syndrome in pregnancy and is moderately effective in the prevention of pre-eclampsia in high-risk obstetric patients.¹² After gestational week 20, all NSAIDs (except aspirin ≤ 100 mg/day) can cause constriction of the ductus arteriosus and impair foetal renal function, and they should be withdrawn (Table 14). Colchicine is rather contraindicated, although in women with Familial Mediterranean Fever no adverse events on fertility, pregnancy or fetal or child development have been reported even during prolonged exposure to the drug.¹²

RECURRENT PERICARDITIS

Definition

Recurrent pericarditis is diagnosed when there is a documented first attack of acute pericarditis, a symptom-free interval of 4-6 weeks or longer, and evidence of either recurrence or continued activity of pericarditis by means of recurrent pain, and 1 or more of the following signs: fever, pericardial friction rub, electrocardiographic changes, echocardiographic evidence of pericardial effusion, and elevations in the white blood cell count or erythrocyte sedimentation rate or C-reactive protein. **Incessant** pericarditis refers to persistent pericarditis lasting more than 4-6 weeks but less than 3 months. **Chronic** is pericarditis lasting more than 3 months.¹²

Presentation

Early high-dose steroids, a lack of colchicine, and elevated high-sensitivity CRP are associated with the development of complicated pericarditis.¹⁸ Recurrences occur in up to 30% of patients with acute pericarditis (15% in those treated with colchicine),²² and usually occur less than 6 weeks after discontinuation or reduction of treatment but may also appear as late as 20 months after the initial attack.⁸ They are often seen at discontinuation of or attempts to wean patients from anti-inflammatory treatment. Prognosis is good in idiopathic cases and there is no risk of constriction.

Therapy

Aspirin, or a **NSAID**, are given for at least 4 weeks. Doses are as for acute pericarditis with gradual tapering by 50% of the dose every 1-2 weeks. **Colchicine** is added for up to 6 months.^{1, 23} Long-term colchicine is usually well tolerated with rare discontinuation required for diarrhoea. Hepatotoxicity and myelosuppression may occur in patients with chronic renal failure. In truly refractory cases, triple therapy with **aspirin or NSAID, colchicine and corticosteroids**, such as prednisone 0.25-0.5 mg/kg/day with rapid tapering to 25 mg/day, and then gradual tapering by 20% of the dose every 1-2 weeks if the patient is asymptomatic and the CRP normal, should be administered. 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/day of prednisone or equivalent. The risk of relapse approaches 20% in 18 months.²²

Alternatively, **azathioprine**, 1 mg/kg/day given once daily or divided twice daily, gradually increased till 2–3 mg/kg/day, intravenous immunoglobulin (IVIG) 400–500 mg/kg/day for 5 days, or 1 g/kg/day for 2 days, eventually repeated every 4 weeks. **Anakinra** (a recombinant IL-1 β receptor antagonist,) 1–2 mg/kg/day up to 100 mg once daily subcutaneously, or intrapericardial triamcinolone, may be tried.²⁴ **Rilonacept**, an interleukin-1 α and interleukin-1 β cytokine trap led to rapid resolution of recurrent pericarditis episodes and to a significantly lower risk of pericarditis recurrence than placebo (RHAPSODY trial).²⁵ Rarely, a pericardial window or even pericardiectomy may be needed.²⁶ Goflikicept, an interleukin (IL)-1 α and IL-1 β inhibitor has also provided favorable preliminary results.²⁷

Noncardiac Surgery

Recommendations on non-cardiac surgery in Table 13.

Pregnancy

Recommendations on non-cardiac surgery in Table 14.

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