Diagnosis and treatment of pericarditis

Massimo Imazio,[1] Fiorenzo Gaita[2]

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2014-306362).

[1]Cardiology Department, Maria Vittoria Hospital and University of Torino, Torino, Italy
[2]University Division of Cardiology, Department of Medical Sciences, University of Torino, Torino, Italy

Correspondence to
Massimo Imazio, MD, FESC, Cardiology Department, Maria Vittoria Hospital and Department of Medical Sciences, University of Torino, Torino, Italy. Via Luigi Cibrario 72, 10141 Torino, Italy, massimo_imazio@yahoo.it, massimo.imazio@unito.it

Published Online First
8 April 2015

To cite: Imazio M, Gaita F. *Heart* 2015;**101**: 1159–1168.

Curriculum topic: Pericardial disease

INTRODUCTION

Classification and definition

Pericarditis is an inflammatory disease of the pericardium, which may have infectious or non-infectious causes, and is manifested by a combination or signs (ie, pericardial rubs, electrocardiographic changes and pericardial effusion), symptoms (mainly chest pain but possible additional symptoms such as dyspnoea) and usually elevation of markers of myocardial inflammation (ie, protein C reactive).[1–6] A concomitant myocardial involvement has been described in about one-third of patients with acute pericarditis and it is due to overlapping aetiological agents for pericarditis and myocarditis. In clinical practice it is often detected by elevation of markers of myocardial lesion (ie, troponins) assessed for the differential diagnosis with an acute coronary syndrome. These cases usually with preserved left ventricular function are commonly labeled as myopericarditis.[7 8]

The disease may present as an isolated process or as a part of another disease with pericardial involvement (ie, systemic inflammatory disease and lung cancer) thus involving different medical specialties (ie, cardiology, internal medicine, rheumatology, oncology and nephrology).[6] Specific terminology has been adopted in clinical studies as well as guidelines and reviews and will be briefly reviewed in order to promote standardised definitions.

Acute pericarditis is the first attack of pericarditis, generally occurring with an acute onset of symptoms. Treatment of the episode generally lasts for 4–6 weeks, considering the attack dose and drug tapering. If the patient does not reach a remission and the disease lasts several weeks or months without a symptoms-free interval of 4–6 weeks, the term *incessant pericarditis* is adopted. If the disease reappears after a symptom-free interval of 4–6 weeks, the term *recurrent or relapsing pericarditis* is given.[9 10]

Pericarditis lasting for more than 3 months is considered 'chronic pericarditis', while the term 'subacute pericarditis' applies for cases with a disease lasting more than 4–6 weeks but <3 months. All these definitions have been arbitrarily defined by experts but the rationale for all these definitions is to consider the completion of therapy after the attack (4–6 weeks) and distinguish true recurrences from episodes without resolution (recurrent vs incessant and chronic).[9 11]

Constrictive pericarditis is the result of scarring and consequent loss of the normal elasticity of the pericardial sac with impaired filling. Pericardial constriction is typically chronic, but variants include subacute, transient and occult constriction.[12] When a pericardial effusion (often with cardiac tamponade) coexists with a constrictive pericardium, the term *effusive-constrictive pericarditis* is adopted.[13]

Learning objectives

1. Review the definitions, classification and aetiology of pericarditis.
2. Describe the clinical presentation, diagnostic criteria and work-up, laboratory and imaging findings of pericarditis.
3. Review and describe the contemporary medical, interventional and surgical therapies, the prevention and prognosis of pericarditis.

Epidemiology, pathophysiology and aetiology

Acute pericarditis is one of the most common disorders involving the pericardium. Epidemiologic studies are lacking, and the exact incidence and prevalence of acute pericarditis are unknown. It is a common differential diagnosis in patients presenting with acute chest pain. In an observational study from an urban area in Northern Italy the incidence of acute pericarditis was 27.7 cases per 100 000 persons per year.[14]

The aetiology of pericarditis is varied and it may include infectious and non-infectious causes (box 1).[1–6] In developed countries with a low prevalence of tuberculosis (TB), more common causes include viral infections, systemic inflammatory diseases and cancer (especially lung and breast cancer or lymphomas and leukaemia).[5 11] In developing countries with a high prevalence of TB, TB, often with concomitant HIV-infection, is the more common cause of the disease (about two of three cases in Sub-Saharan Africa).[15 16] On this basis, the epidemiological background has to be considered when evaluating a patient with pericarditis.[17]

History taking and clinical examination

The onset of symptoms is generally acute for viral and immune-mediated forms, while it may be subacute in other forms. Viral aetiologies, in particular, may be preceded by 'flu-like' respiratory or gastrointestinal symptoms. Patients with a known autoimmune disorder or malignancy may present with signs or symptoms specific to their underlying disorder.

A previous history of TB or current TB infection, as well as the origin from a geographical area with a high prevalence of TB, should alert the clinician on the possible correlation between pericarditis and/or pericardial effusion and TB.[15–17]

The major clinical manifestations of acute pericarditis include:

1. *Chest pain*—typically sharp and pleuritic, improved by sitting up and leaning forward. This position (seated, leaning forward) tends to

Box 1 Aetiology of pericarditis divided according to infectious and non-infectious causes

Infectious causes:
- *Viral* (especially coxsackievirus, echovirus, Ebstein-Barr Virus (EBV), Cytomegalovirus (CMV), adenovirus, parvovirus B19 and human herpes virus 6: possible overlap with etiologic viral agents of myocarditis)
- *Bacterial* (especially tuberculosis, and *Coxiella burnetii*, other bacterial are rare)
- *Fungal* (very rare: histoplasma more likely in immunocompetent patients, aspergillosis, blastomycosis, *Candida* more likely in immunosuppressed host)
- *Parasitic* (very rare: echinococcus, toxoplasma)

Non-infectious causes:

Autoimmune and autoinflammatory:
- *Pericardial injury syndromes* (postmyocardial infarction syndrome, postpericardiotomy syndrome, posttraumatic including iatrogenic trauma).
- *Systemic autoimmune and autoinflammatory diseases* (especially systemic lupus erythematosus, Sjögren syndrome, rheumathoid arthritis, systemic sclerosis, systemic vasculitides, Behçet syndrome, Sarcoidosis, Familial Mediterranean Fever and tumour necrosis factor receptor-associated periodic syndrome)

Neoplastic:
- *Primary tumours* (rare, above all pericardial mesothelioma)
- *Secondary metastatic tumours* (common, above all lung and breast cancer, leukaemia, lymphoma, melanoma-rare, cancer of contiguous anatomical structures, ie, oesophagus)

Metabolic (uraemia, myxoedema and other rare)

Posttraumatic
- *Direct injury* (penetrating thoracic injury, oesophageal perforation and iatrogenic)
- *Indirect injury* (non-penetrating thoracic injury, radiation injury)
- *Drug-related* (*procainamide*, *hydralazine*, *isoniazid* and *phenytoin* as lupus-like syndrome, *penicillins* as hypersensitivity pericarditis with eosinophilia, *doxorubicin* and *daunorubicin* (often associated with a cardiomyopathy, may cause a pericardiopathy)
- *Postinterventions*: for example, coronary percutaneous intervention, pacemaker lead insertion and radiofrequency ablation)

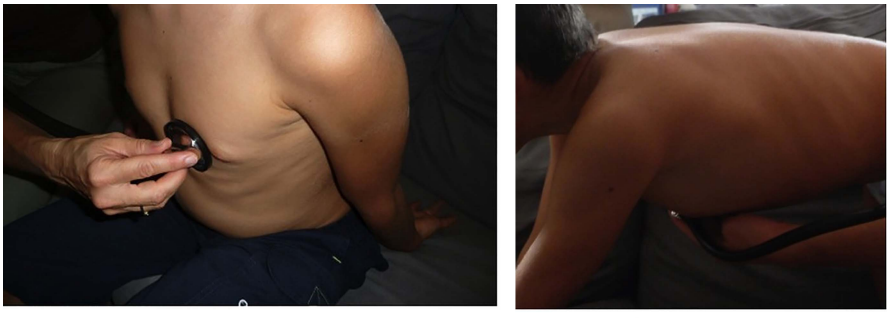
reduce pressure on the parietal pericardium, particularly with inspiration. It is reported in >90% of cases. It is provoked by the increased attrition and inflammation of pericardial layers. It is a visceral pain that may be sometimes difficult to differentiate from ischaemic chest pain.[5 6 18 19]

2. *Pericardial friction rub*—a superficial scratchy or squeaking sound best heard with the diaphragm of the stethoscope over the left sternal border (figure 1), it has been reported in one-third of patients (see online supplemental audio file). Friction rubs tend to vary in intensity and can come and go over, thus repeated auscultation may be necessary. The classic friction rub consists of three phases, corresponding to movement of the heart during atrial systole (absent in cases with atrial fibrillation), ventricular systole and the rapid filling phase of early ventricular diastole. Some rubs may have only one or two components. They are considered the result of an increased attrition of inflamed pericardial layers.[19 20]
3. *ECG changes*—new widespread ST elevation or PR depression (figure 2).[19 20]
4. *Pericardial effusion* (figure 3) that has been reported in about 60% of cases and it is usually mild.[19 20]

ECG

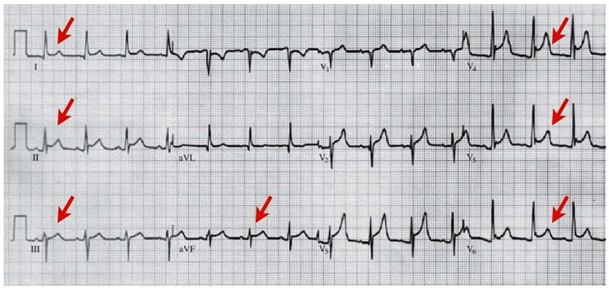
ECG changes occurring during pericarditis essentially imply *inflammation of the myocardium close to the epicardium*, since the pericardium itself is electrically inert. Thus, a mild degree of subepicardial myocardial involvement is a common finding due to the overlapping aetiological agents of pericarditis and myocarditis.[8 11] This also explains the absence of ECG changes in patients with uraemic pericarditis, where the serosal inflammatory involvement is not associated with myocardial involvement. The classical ECG evolution includes four stages of changes (figure 2) and it is reported in no more than 60% of cases:[19–21]
- *Stage 1* (acute phase within hours to few days) is characterised by diffuse ST elevation (typically concave up) and depression of the PR segment;
- *Stage 2*, typically seen in the first week, is characterised by normalisation of the ST and PR segments;
- *Stage 3* is characterised by the development of diffuse T wave inversions, after the ST segments have become isoelectric;
- *Stage 4* is represented by normalisation of the ECG or indefinite persistence of T wave inversions.

The observation time and anti-inflammatory therapy may hasten or delay the ECG evolution. Thus a patient with a very early presentation or after efficacious treatment may have a normal ECG, while patients with delayed presentations or chronic evolution may have T waves inversion instead of ST segment elevation.

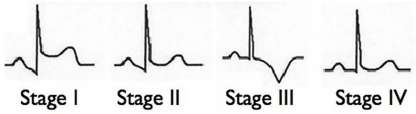


Panel A Panel B

Figure 1 The intensity of the rub frequently increases after application of firm pressure with the diaphragm, during suspended respiration, and with the patient leaning forward (A) or resting on elbows and knees (B).



Panel A



Panel B

Figure 2 (A) Traditional electrocardiographic changes are characterised by diffuse ST elevation (typically concave up) with reciprocal ST depression in leads aVR and V1. At the onset there is also a possible atrial current of injury, reflected by elevation of the PR segment in lead aVR and depression of the PR segment in other limb leads and in the left chest leads, primarily V5 and V6. The TP segment is recommended as the baseline for comparison when measuring both PR and ST segment changes in acute pericarditis. (B) Typical ECG evolution of pericarditis in four stages (see text for explanation).

Sustained arrhythmias are uncommon in acute pericarditis, thus, the presence of atrial or ventricular arrhythmias is suggestive of concomitant myocarditis or an unrelated cardiac disease.[7] Main ECG differential diagnosis includes acute coronary syndromes with ST-segment elevation and early repolarisation.

The ST segment elevation in acute pericarditis rarely exceeds 5 mm, and usually retains its normal concavity. Moreover it is widespread and not associated with reciprocal changes, q waves, QRS widening and QT prolongation.[22]

In acute pericarditis, the ratio of ST elevation to T wave amplitude in lead V6 usually exceeds 0.24 (positive and negative predictive values are both 100%), and this ECG sign has the greatest diagnostic accuracy for the differential diagnosis with early repolarisation.[19–21]

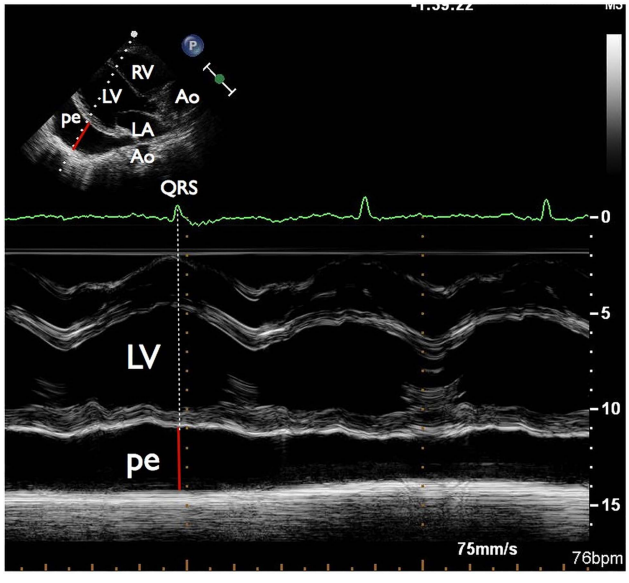


Figure 3 Echocardiographic semiquantitative assessment of pericardial effusion. The largest effusion is considered in different echocardiographic views (including off-axis views). The largest telediastolic diameter of the effusion is measured. According to the telediastolic echo-free space, the pericardial effusion is defined as *mild* if <10 mm, *moderate* from 10 to 20 mm, and *large* if >20 mm. A large effusion is a *red flag* for pericarditis suggesting an increased risk of a non-viral, non-idiopathic aetiology and complications during follow-up., LA, left atrium; Ao, aorta; pe, pericardial effusion.

Imaging and laboratory and findings

Echocardiogram—Transthoracic echocardiography provides the essential diagnostic imaging for the detection of pericardial effusion, its semiquantitative assessment (figure 3) and haemodynamic effects on the heart (ie, diagnosis of cardiac tamponade and constrictive physiology).[19 23] Pericardial effusion is reported in no more than 60% of cases and it is generally mild.[19–21]

Chest X-ray—Chest radiography is typically normal in patients with acute pericarditis. An enlarged cardiac silhouette may be detected with large effusion (water bottle sign; figure 4). On this basis, pericarditis should be considered in the evaluation of a patient with new and otherwise unexplained cardiomegaly, especially with clear lung fields.[19–21]

Biomarkers—Pericarditis may be associated with increases in serum biomarkers of myocardial injury (ie, cardiac troponin I or T) in about one-third of cases as expression of concomitant myocarditis. In this setting with an usual preserved ventricular function, the prognosis of these mixed form with prevalent pericarditis (also referred as *myopericarditis*) is good and, unlike acute coronary syndromes, troponin does not seem a negative prognostic marker.[24] Since pericarditis is an inflammatory disease, laboratory signs of inflammation (ie, the white blood cell count, erythrocyte sedimentation rate and serum C -reactive protein concentration, CRP) can be detected in the majority of cases. On this basis and according to prospective cohort observations, especially CRP may be considered to confirm the diagnostic suspicion of pericarditis and to monitor the disease activity in order to individualise the appropriate treatment length.[25]

Genetics

Familial occurrence of cases with pericarditis has been described for recurrent pericarditis and genetic factors are undoubtedly important to affect the individual predisposition to the disease and the development of recurrences. For instance, it has been reported a genetic predisposition in patients with systemic lupus erythematosus, as well as autoinflammatory diseases, such as familial mediterranean fever and the tumour necrosis factor receptor-1-associated periodic syndrome.[26 27]

Diagnostic work-up

When to suspect pericarditis and differential diagnosis

Pericarditis should be suspected in a patient with a history of characteristic pleuritic chest pain, often preceded by a flu-like syndrome few weeks before,

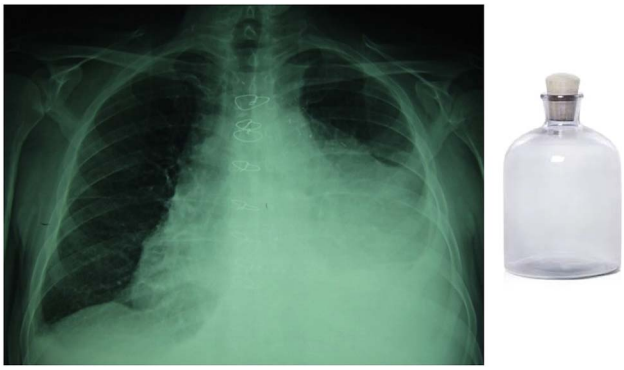


Figure 4 On chest X-ray, enlarged cardiac silhouette due to postoperative pleuro-pericardial effusions. An enlarged cardiac silhouette is detected when at least 200 mL of pericardial fluid accumulate. This shape is also named *water bottle sign or configuration.*

and confirmed by the presence of pericardial rubs, suggestive of ECG changes and pericardial effusion on echocardiography.[4 6 10 19–21] Elevation of inflammatory markers (eg, CRP) provides additional supportive evidence.[25] For rare complicated cases, when the diagnosis is still doubtful, additional non-invasive imaging techniques, such as CT and cardiac magnetic resonance may be useful since the inflamed pericardium can be seen as thickened and enhanced by these imaging techniques (figure 5).[23] Commonly accepted clinical criteria for the diagnosis are reported in table 1. Differential diagnosis should include alternative causes of chest pain and especially acute coronary syndromes.

Red flags, triage and aetiology search

At presentation, specific clinical characteristics are associated with an increased risk of a specific aetiology and complication during follow-up.[28]

Features of acute pericarditis associated with a higher risk especially include:

- Fever (>38°C or 100.4°F)
- Subacute course
- Large pericardial effusion (echo-free space >20 mm)
- Cardiac tamponade
- Failure to respond to aspirin/non-steroidal anti-inflammatory drug (NSAID) therapy.

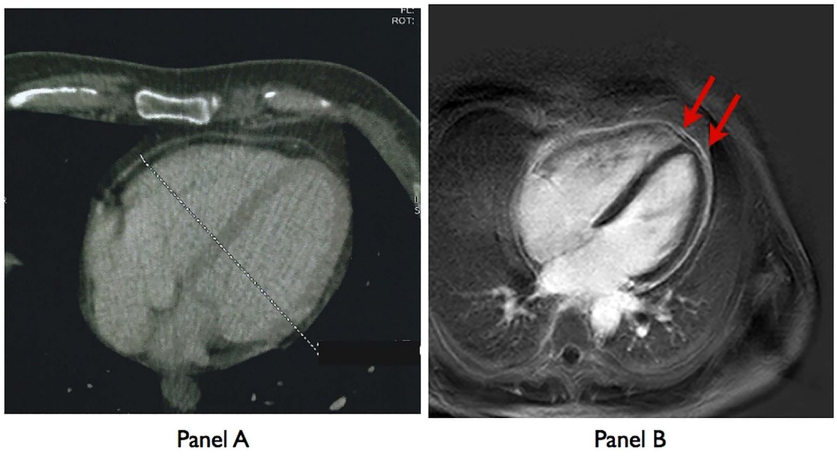
Such features represent 'red flags' that should alert the clinician to admit the patient and perform an aetiological search essentially to rule out most common causes of pericarditis: TB or other bacterial causes, systemic inflammatory diseases, secondary neoplastic involvement of the pericardium (table 2). On this basis a triage of patient with pericarditis has been proposed (figure 6).[28–30]

Hospital admission is indicated for high-risk patients in order to initiate appropriate therapy and a thorough aetiological evaluation.[3 4 28–30] Female gender may be associated with an increased risk of a systemic inflammatory disease and thus, potentially, more complications during follow-up (hazard ration 1.65).[28] A possible explanation of this finding is the higher frequency of autoimmune aetiologies (above all connective tissue diseases) in women.

The basic diagnostic evaluation includes:

- history and physical examination (to detect pericardial rubs and additional possible signs of a systemic disease that may be responsible for pericarditis);
- basic chemistry (markers of inflammation and myocardial lesion, blood count, creatinine);
- ECG;
- transthoracic echocardiography;
- chestX-ray.

Additional testing should be performed according to the clinical suspicion of a specific aetiology based on history, physical examination, basic chemistry, ECG, echocardiography and chest X-ray, and not randomly. Routine viral studies are no longer recommended, since the yield is low and serological evidence of a recent infection only suggests a recent viral infection with a probable correlation with pericarditis. Definite viral diagnosis would require a pericardial biopsy or pericardial fluid analyses that have no justification in an uncomplicated setting since the management and therapy is not altered and there is no demonstration that a specific antiviral therapy is needed in an immunocompetent patient with pericarditis.[31 32]



Panel A Panel B

Figure 5 The inflamed pericardium can be seen as thickened (A on CT) and enhanced either on CT or cardiac magnetic resonance (B; see red arrows). These second level imaging techniques are especially useful for doubtful presentations to achieve the diagnosis of pericarditis.

Table 1 Diagnostic criteria for pericarditis: at least two of four main clinical criteria are required

1.	*Chest pain*—typically sharp and pleuritic, improved by sitting up and leaning forward
2.	*Pericardial friction rubs*
3.	*ECG changes*—new widespread ST elevation or PR depression
4.	*Pericardial effusion*
*	Elevation of markers of inflammation (ie, C-reactive protein)
*	Thickening and enhancement of the pericardium by CT and/or cardiac magnetic resonance(CMR)

Supportive findings* include: elevation of markers of inflammation and evidence of pericardial inflammation by a second level imaging technique such as CT and CMR.

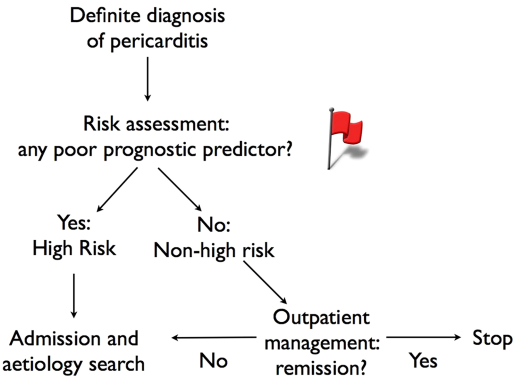


Figure 6 Proposed triage for pericarditis (see text for explanation).

Specific recommendations based on the clinical suspicion of a specific aetiology are reported in table 3.

Such approach is consistent with current available guidelines: national guidelines (2000 Spanish guidelines,[33] 2013 Brazilian guidelines[34]), 2004 European guidelines[35] and a 2013 expert consensus statement from the American Society of Echocardiography.[23]

Multimodality evaluation and team working

Multimodality imaging is an integral part of modern management for pericarditis and pericardial diseases. Among multimodality imaging tests, echocardiography is most often the first-line test, followed by CMR and/or CT (table 4).[23 36 37]

In the presence of specific aetiologies (systemic inflammatory diseases, renal diseases, TB or a specific infectious agent and cancer), consultation and team working with different and appropriate specialty consultants may be required for appropriate diagnostic steps and subsequent therapy.[29]

Therapy

Medical therapy

The medical therapy should be targeted as much as possible at the aetiology. However, a significant proportion of patients do not reach the identification of the cause since viral and immune-mediated causes are often difficult to detect. Such cases are usually named as 'idiopathic pericarditis'. The term itself states that the aetiology is unknown but it is clinically meaningful if this diagnosis is reached after appropriate exclusion of bacterial infections, systemic diseases and cancer since its prognosis is good and therapy well defined. For idiopathic, viral pericarditis and those associated with a systemic inflammatory disease (in the absence of specific rheumatologic indications), the mainstay of therapy is aspirin or a NSAID, especially ibuprofen (table 5). Anti-inflammatory treatment provides symptom control, faster achievement of remission and reduction of the subsequent recurrences.[4 11 38–42]

Full attack doses (table 5) should be provided every 8 h in order to have a better control of symptoms through the whole day and maintained till complete symptom resolution and normalisation of markers of inflammation (ie, CRP).[25 43] Corticosteroid therapy may be indicated for specific indications (pregnancy, systemic inflammatory disease with a defined indication), contraindications to aspirin/NSAID and failure of at least more than one NSAID. Low to moderate doses of corticosteroids (ie, prednisone 0.2–0.5 mg/kg/day) are warranted and should be maintained for several weeks till complete symptoms resolution and normalisation of markers of inflammation with a slow tapering that is performed every 2–4 weeks only after remission (table 5).[44]

Colchicine without loading doses and using weight-adjusted doses should be provided on top of aspirin or a NSAID or a corticosteroid to hasten the control of the disease and halve the recurrence rate in the absence of contraindications (essentially hypersensitivity to colchicine, severe renal impairment, severe liver diseases and pregnancy).[10 45–47]

Table 2 Final aetiological diagnosis in major published unselected series of acute pericarditis (modified from Imazio *et al*[11])

Patients years	Permanyer-Miralda *et al* (n=231), 1977–1983	Zayas *et al* (n=100), 1991–1993	Imazio *et al* (n=453), 1996–2004	Reuter *et al** (n=233), 1995–2001
Geographic setting	Western Europe	Western Europe	Western Europe	Africa
Idiopathic	199 (86.0%)	78 (78.0%)	377 (83.2%)	32 (13.7%)
Specific aetiology:	32 (14.0%)	22 (22.0%)	76 (16.8%)	201 (86.3%)
Neoplastic	13 (5.6%)	7 (7.0%)	23 (5.1%)	22 (9.4%)
Tuberculosis	9 (3.9%)	4 (4.0%)	17 (3.8%)	161 (69.5%)
Autoimmune	4 (1.7%)	3 (3.0%)	33 (7.3%)	12 (5.2%)
Purulent	2 (0.9%)	1 (1.0%)	3 (0.7%)	5 (2.1%)

*Based on pericardial effusions.

Table 3 Specific diagnostic testing based on the clinical suspicion of a specific aetiology of pericarditis

Suspected aetiology	Suggested diagnostic testing
Tuberculous pericarditis	*Definite diagnosis*: isolation of bacteria from pericardial fluid (pericardiocentesis) or tissue (pericardial biopsy). *Probable diagnosis*: detection of specific biomarkers in pericardial fluid (adenosine deaminase, interferon gamma) or evidence of active TB elsewhere (exclude TB by testing sputum, urine, gastric aspirate; detection of typical lymphoadenopathies on chest X-ray and CT; consider similar testing for pleural fluid if available) and/or good response to antituberculosis chemotherapy.
Purulent pericarditis	Blood cultures and pericardiocentesis with cultures from pericardial fluid.
Neoplastic pericarditis	*Definite diagnosis:* isolation of neoplastic cells from pericardial fluid (pericardiocentesis and cytology) or tissue (pericardial biopsy). *Probable diagnosis:* detection of specific biomarkers in pericardial fluid (tumour markers) or masses in the presence of a possible related cancer. Additional testing to detect the primary cancer (especially lung and breast cancer or leukaemia and lymphomas, more rarely other tumours ie, melanoma or other).
Systemic inflammatory disease	Autoantibodies testing and rheumatologic evaluation.

Using correct indications and low doses, the most common side effect is gastrointestinal intolerance (about 8% of cases). Appropriate monitoring of the therapy is reached through chemistry (renal function, transaminases, creatine kinase and blood count) after 1 month and then in case of new symptoms or signs that may suggest and adverse event or a possible drug interaction. For colchicine the most important drug interactions include statins (both drugs are myotoxic), macrolides (impair colchicine clearance) and cyclosporine. Children <5 years, elderly >65–70 years and patients with renal impairment require dose adjustment (table 6).[10 45–48]

Alternative treatments include azathioprine[49] and other immunosuppressive drugs, intravenous (iv) human immunoglobulins (400–500 mg/kg iv daily for 5 days with possible repeated cycle for additional recurrences)[50] or biological agents (ie, anakinra 1 to 2 mg/Kg/day up to 100 mg/day subcutaneously or sc for several months).[51 52] Such treatments are supported by weaker evidence (case reports, series or retrospective studies, expert opinions) and should be considered in case of several failures of conventional anti-inflammatory therapies and colchicine (more severe cases may achieve control of symptom by combining aspirin or a NSAID plus a low to moderate dose of a corticosteroid and colchicine with combination therapies that are similar to those cardiologists use to control symptoms in stable angina with several drugs). These true refractory cases are no more than 5% of patients with recurrent pericarditis.[53]

Adjunctive measures include restriction of physical activities beyond sedentary life till complete symptoms resolution and normalisation of CRP, ECG and echocardiography. For athletes, an expert consensus identified the need for a minimal 3 months period of stopping competitive activities until remission and normalisation of findings.[54 55]

Interventional treatments and surgical therapy

Most patients with acute pericarditis can be managed effectively with medical therapy alone. On occasion, however, patients may require invasive therapies for:

1. cardiac tamponade;
2. a moderate to large pericardial effusion, particularly if haemodynamically significant and symptomatic or refractory to medical therapy;
3. suspicion of a neoplastic or bacterial aetiology;
4. evidence of constrictive or effusive-constrictive pericarditis.

Percutaneous and surgical techniques may be considered for such patients. Echo and or fluoroscopy guided pericardiocentesis is indicated for initial drainage of pericardial fluid. Echo-guided pericardiocentesis is the simplest monitoring that is available in the emergency and urgency setting, as well as outside the cath laboratory. Echocardiography allows the detection of the best puncture site, where pericardial effusion is largest and closest to the thorax. The adjunct of prolonged catheter drainage is a

Table 4 Findings, strengths and weaknesses of main imaging techniques for pericarditis

Feature	Echocardiography	CT	Cardiac magnetic resonance
What can offer	Evaluation of pericardial effusion Assessment of cardiac tamponade and constriction Evaluation of myocardial involvement	Assessment of pericardial calcifications and thickening Evaluation of concomitant diseases	Tissue characterisation Assessment of thickening and constriction Evaluation of myocardial involvement
Strengths	Availability Low cost Portable Can be performed on urgent basis Can evaluate effects of respiration	Evaluation of calcifications Evaluation of associated pleuropulmonary and extra-thoracic diseases	Tissue characterisation Evaluation of inflammation and myocardial involvement
Weaknesses	Limited window and narrow field of view Limitations according to comorbidities (COPD, obesity, postoperative) Operator-dependent Limited tissue characterisation	Use of ionising radiation and iodinated contrast Require breath-hold and cannot evaluate respiratory effects Not able to assess unstable patients or those with arrhythmias	Time-consuming High costs Limited availability Require stable patients and rhythms Calcifications not well evaluated Patients with severe renal impairment and PM may be contraindicated

COPD, chronic obstructive pulmonary diseases; PM, pacemaker.

Table 5 Attack doses for medical therapy of pericarditis

Drug	Attack dose	Treatment length
First level drugs:		
Aspirin	750–1000 mg every 8 h	1–2 weeks till remission than tapering*
NSAID:		
Ibuprofen	600 mg every 8 h	idem
Indomethacin	50 mg every 8 h	idem
Colchicine	0.5 mg twice daily (>70 kg), otherwise 0.5 mg	3 months (acute) 6–12 months (recurrent)
Second level drugs:		
Corticosteroids eg, prednisone	0.2–0.5 mg/kg/day	2 weeks (acute) 2–4 weeks (recurrent) till remission than slow tapering†
Third level drugs:		
Azathioprine	1.5–2.5 mg/kg	Several months
Iv human Ig	400 to 500 mg/kg iv	5 days; may be repeated
Biological agents: ie, anakinra	1–2 mg/kg sc up to 100 mg/day	Several months

Monitoring of disease activity is based on weekly assessment of C-reactive protein (CRP). Safety monitoring of therapy is performed with assessment of symptoms and signs related to toxicity and chemistry assessment (essentially transaminases, creatine kinase, blood count, creatinine) at least at 2–4 weeks and then according to clinical evolution, potential interfering drugs.
*Remission is reached with symptoms regression, normalisation of CRP and other testing (ie, ECG) then tapering may be considered to reduce the subsequent recurrence risk.
†Tapering of corticosteroids is performed only after remission and it is very slow: that is, 2.5 mg every 2–4 weeks according to the severity of the case.
NSAID, non-steroidal anti-inflammatory drugs.

potentially effective means of preventing fluid reaccumulation. The mechanism by which this occurs is probably more related to the obliteration of the pericardial space following inflammation provoked by the catheter, rather than fluid drainage itself.

Table 6 Major contraindications, interactions for colchicine and dose adjustment

Feature	Data
Major contraindications	Concomitant use of a P-glycoprotein (P-gp) or strong CYP3A4 inhibitor in presence of renal or hepatic impairment Severe renal impairment Severe liver disease Pregnancy
Major interactions	*HMG-CoA reductase inhibitors*: Colchicine may enhance the myopathic (rhabdomyolysis) effect of HMG-CoA reductase inhibitors. Colchicine may increase the serum concentration of HMG-CoA reductase inhibitors. *Strong CYP3A4 inhibitor* (eg, clarithromycin, itraconazole, ketoconazole): May increase the serum concentration of colchicine. Management: Colchicine is contraindicated in patients with impaired renal or hepatic function who are also receiving a strong CYP3A4 inhibitor. In those with normal renal and hepatic function, reduce colchicine dose, generally by 50%. *P-gp inhibitor* (eg, cyclosporine, ranolazine): May increase the serum concentration of colchicine. Colchicine distribution into certain tissues (eg, brain) may also be increased. Management: colchicine is contraindicated in patients with impaired renal or hepatic function who are also receiving a P-gp inhibitor. In those with normal renal and hepatic function, reduce colchicine dose
Dose-adjustment:	
Children <5 years	Reduce daily dose by 50%
Elderly >65–70 years	Reduce daily dose by 50%
Renal failure:	
–	CrCl 30 to 60 mL/min: Monitor closely for adverse effects; dose reduction by 50%. CrCl 15 to 30 mL/min: Consider alternative drug or to avoid. If used: Initial dose: 0.5 mg every 2 days; very close monitor for adverse effects. Dialysis or CrCl <15 mL/min: do not use

Impaired renal function and advanced age are major risk factors for the appearance of side effects and dose adjustments may be required generally halving the doses or avoiding the association.
Concurrent use of colchicine and P-gp or strong CYP3A4 inhibitors is **contraindicated** in renal and hepatic impairment.

Catheter drainage may be required for several days and the catheter should not be removed until drainage is less than 20–30 mL/24 h.[56]

Pericardial biopsy is generally performed as a part of a therapeutic procedure or as a diagnostic procedure in patients with an illness lasting more than 3 weeks despite treatment without a definite diagnosis.[57–59]

Removal of the pericardium (pericardiectomy) may be considered for frequent and highly symptomatic recurrences of pericarditis resistant to medical treatment, and is indicated for persistent chronic constrictive pericarditis or recurrent cardiac tamponade. The efficacy of pericardiectomy in the management of recurrent idiopathic pericarditis is especially supported by a retrospective study from the Mayo Clinic.[60] Such surgical treatment may be an option in well-experienced tertiary referral centres, since pericardiectomy is a long and demanding intervention that should be complete as much as possible and requires an experienced surgeon to achieve the best outcomes.

Surgical decompression of the pericardium (also known as pericardiotomy, pericardiostomy and 'window' pericardiectomy) can be achieved either by conventional heart surgery or video-assisted thoracoscopy. These techniques may result in a lower incidence of effusion recurrence compared with pericardiocentesis and prolonged catheter drainage. However, surgical experiences are not always concordant, and the efficacy of these procedures remains largely unproven.

Less-invasive options (eg, balloon pericardiotomy) for the management of recurrent symptomatic pericardial effusions are mainly derived from the experience of management of neoplastic pericardial effusions and include prolonged catheter drainage and the creation of the so-called 'pericardial window.' These techniques, which involve inserting balloon catheters into the pericardial space using a subxiphoid approach under fluoroscopic or echocardiographic guidance, are highly successful in preventing recurrent effusions, especially for patients with a reduced life expectancy since reaccumulation of fluid may occur with longer follow-up.[57–59]

Prevention and outcomes

Patients with acute idiopathic or viral pericarditis have a good long-term prognosis.[24 61–63] Cardiac tamponade rarely occurs in patients with acute idiopathic pericarditis and is more common in patients with a specific underlying aetiology such as malignancy, TB or purulent pericarditis. Constrictive pericarditis may occur in about 1% of patients with acute idiopathic pericarditis, and is also more common in patients with a specific aetiology. The risk of developing constriction is related to the aetiology and not to the number of recurrences (low as about 1% for viral/idiopathic pericarditis, intermediate as about 2 to 4% for systemic inflammatory diseases and neoplastic pericardial diseases, and high as about 20 to 33% for bacterial aetiologies).[61 62]

Key points

- Pericarditis is generally caused by viral infections, systemic inflammatory diseases and cancer (especially lung and breast cancer or lymphomas and leukaemia) in developed countries (low prevalence of tuberculosis [TB]). TB is the major cause in developing countries (often associated with HIV infection).
- The clinical diagnosis is based on the combination of 'pericarditic chest pain' plus at least one sign: pericardial rubs, ECG changes and pericardial effusion on echocardiography.
- Markers of inflammation (especially C reactive protein) should be considered to confirm the diagnosis, to monitor the disease and to individualise the duration of treatment.
- Hospital admission is indicated for high-risk patients (fever >38°C (100.4°F)), subacute course, large pericardial effusion >20 mm, cardiac tamponade and failure to respond to aspirin/non-steroidal anti-inflammatory drug [NSAID] therapy) in order to initiate a thorough aetiological evaluation and evaluate the response to therapy.
- The basic diagnostic evaluation includes: history and physical examination, basic chemistry (markers of inflammation and myocardial lesion, blood count, creatinine), ECG, transthoracic echocardiography and chest X-ray.
- Pericardiocentesis is indicated for cardiac tamponade, moderate to large pericardial effusions, if symptomatic and persistent despite medical therapy, or for suspicion of neoplastic or bacterial aetiology.
- The mainstay of therapy is aspirin or a NSAID (especially ibuprofen) plus colchicine to reduce recurrences. For specific causes (eg, cancer, TB) medical therapy should be targeted.
- Adjunctive measures include restriction of physical activities beyond sedentary life till remission.

Approximately one-third of patients with pericarditis who are not treated with colchicine develop either recurrent or incessant disease.[10 45 46] Recurrences are the most common and troublesome complication following pericarditis. Immune mechanisms appear to be of primary importance in the majority of cases. Risk factors for recurrent pericarditis include lack of response to NSAID, the use of corticosteroid therapy (probably for impaired clearance of an infectious agent) and inappropriate pericardiotomy or creation of a pericardial window. The only proven means to prevent recurrences is offered by limiting the use of corticosteroids and adding colchicine on top of standard anti-inflammatory therapy.[39 44 47]

Future perspectives

Ongoing basic research is needed to clarify the mechanism responsible for recurrences. Additional studies are needed to improve the diagnostic capabilities to identify specific aetiologies such as bacterial causes (especially TB) and cancer. For therapy, the role of new and emerging treatments (ie, azathioprine, intravenous human immunoglobulins and biological agents) has to be proved, and safety and efficacy evaluation requires additional studies especially multicentre controlled randomised studies. Moreover new updated European guidelines on the management of pericardial diseases are warranted after the first ones issued in 2004.[35]

SUMMARY AND CONCLUSIONS

In conclusion, pericarditis is a common disease in clinical practice. Appropriate diagnostic criteria have been proposed and there are available tools for the triage and to guide admission and aetiological search. Therapy should be targeted as much as possible at the aetiology. For most cases the mainstay of therapy is aspirin or a NSAID plus colchicine in order to fasten the response and prevent recurrences. The prognosis is related to the aetiology and is relatively benign in idiopathic and viral forms despite recurrences that are the most common complications and may affect the quality of life.

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Contributors All authors have contributed to the manuscript, including research of the literature, drafting and reviewing the manuscript, and giving final approval of the manuscript.

Competing interests In compliance with EBAC/EACCME guidelines, all authors participating in Education in Heart have disclosed potential conflicts of interest that might cause a bias in the article. The Department of Cardiology of Maria Vittoria Hospital has received unrestricted research grants from Acarpia (Madeira, Portugal) and FARGIM (Catania, Italy).

Provenance and peer review Commissioned; externally peer reviewed.

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Diagnosis and treatment of pericarditis

Massimo Imazio and Fiorenzo Gaita

Heart 2015 101: 1159-1168 originally published online April 8, 2015
doi: 10.1136/heartjnl-2014-306362