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2015 ESC Guidelines for the diagnosis and management of pericardial diseases

The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)

Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS)

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Abbreviations and acronyms

ADA	adenosine deaminase
AMI	acute myocardial infarction
ANA	anti-nuclear antibody
bFGF	basic fibroblast growth factor
CK	creatine kinase
CMR	cardiac magnetic resonance
CMV	cytomegalovirus
CP	Child–Pugh
CRP	C-reactive protein
CT	computed tomography
EBV	Epstein–Barr virus
ECG	electrocardiogram
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
FDG	fluorodeoxyglucose
FMF	familial Mediterranean fever
GM-CSF	granulocyte-macrophage colony-stimulating factor
HHV	human herpesvirus
HIV	human immunodeficiency virus
HR	hazard ratio
IL	interleukin
IVIG	intravenous immunoglobulins
LCE	late contrast-enhanced
NSAIDs	non-steroidal anti-inflammatory drugs
OR	odds ratio
PAH	pulmonary arterial hypertension
PCIS	post-cardiac injury syndromes
PCR	polymerase chain reaction
PET	positron emission tomography
PPS	post-pericardiotomy syndrome
RCT	randomized controlled trial
spp.	species
SSFP	steady-state free-precession
STIR	short-tau inversion-recovery
TB	tuberculosis
TNF	tumour necrosis factor
TRAPS	tumour necrosis factor receptor-associated periodic syndrome
TSH	thyroid stimulating hormone
Tx	treatment
uIFN-γ	unstimulated interferon-gamma
VEGF	vascular endothelial growth factor

Preamble

Guidelines summarize and evaluate all available evidence on a particular issue at the time of the writing process, with the aim of assisting health professionals in selecting the best management strategies for an individual patient with a given condition, taking into account the impact on outcome, as well as the risk–benefit ratio of particular diagnostic or therapeutic means. Guidelines and recommendations should help health professionals to make decisions in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate.

A great number of Guidelines have been issued in recent years by the European Society of Cardiology (ESC) as well as by other societies and organisations. Because of the impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC Web Site (http://www.escardio.org/Guidelines-&-Education/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines). ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.

Members of this Task Force were selected by the ESC to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management (including diagnosis, treatment, prevention and rehabilitation) of a given condition according to ESC Committee for Practice Guidelines (CPG) policy. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio. Estimates of expected health outcomes for larger populations were included, where data exist. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to predefined scales, as outlined in *Tables 1* and *2*.

The experts of the writing and reviewing panels provided declarations of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. These forms were compiled into one file and can be found on the ESC website (http://www.escardio.org/guidelines). Any changes in declarations of interest that arise during the writing period must be notified to the ESC and updated. The Task Force received its entire financial support from the ESC without any involvement from the healthcare industry.

The ESC CPG supervises and coordinates the preparation of new Guidelines produced by task forces, expert groups or consensus panels. The Committee is also responsible for the endorsement process of these Guidelines. The ESC Guidelines undergo extensive

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Table 1 Classes of recommendations

Classes of recommendations	Definition	Suggested wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Table 2 Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

review by the CPG and external experts. After appropriate revisions the Guidelines are approved by all the experts involved in the Task Force. The finalized document is approved by the CPG for publication in the European Heart Journal. The Guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating.

The task of developing ESC Guidelines covers not only the integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. To implement all guidelines, condensed pocket guidelines versions, summary slides, booklets with essential messages, summary cards for non-specialists, and an electronic version for digital applications (smartphones, etc.) are produced. These versions are abridged and thus, if needed, one should always refer to the full text version, which is freely available on the ESC website. The National Societies of the ESC are encouraged to endorse, translate and implement the ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Surveys and registries are needed to verify that real-life daily practice is in keeping with what is recommended in the guidelines, thus completing the loop between clinical research, writing of guidelines, disseminating them and implementing them into clinical practice.

Health professionals are encouraged to take the ESC Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies. However, the ESC Guidelines do not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

1. Introduction

The pericardium (from the Greek περί, 'around' and κάρδιον, 'heart') is a double-walled sac containing the heart and the roots of the great vessels. The pericardial sac has two layers, a serous visceral layer (also known as epicardium when it comes into contact with the myocardium) and a fibrous parietal layer. It encloses the pericardial cavity, which contains pericardial fluid. The pericardium fixes the heart to the mediastinum, gives protection against infection and provides lubrication for the heart.

Pericardial diseases may be either isolated disease or part of a systemic disease.[1–5] The main pericardial syndromes that are encountered in clinical practice include pericarditis (acute, subacute,

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chronic and recurrent), pericardial effusion, cardiac tamponade, constrictive pericarditis and pericardial masses.[1,4,5] All medical therapies for pericardial diseases are off-label, since no drug has been registered until now for a specific pericardial indication.

1.1 What is new in pericardial diseases?

Pericardial diseases are relatively common in clinical practice and new data have been published since the publication of the 2004 ESC Guidelines on pericardial diseases.[1]

New diagnostic strategies have been proposed for the triage of patients with pericarditis and pericardial effusion and allow the selection of high-risk patients to be admitted as well as when and how additional diagnostic investigations are to be performed.[4–9] Moreover, specific diagnostic criteria have been proposed for acute and recurrent pericarditis in clinical practice.[2,4–15]

Multimodality imaging for pericardial diseases has become an essential approach for a modern and comprehensive diagnostic evaluation. Both the American Society of Echocardiography and the European Association of Cardiovascular Imaging have provided recommendation documents in recent years.[2,3]

The aetiology and pathophysiology of pericardial diseases remain to be better characterized, but new data supporting the immune-mediated pathogenesis of recurrences and new forms related to autoinflammatory diseases have been documented, especially in paediatric patients.[4,6] The first epidemiological data have become available.[7,16]

Age and gender issues are now more evident and clear, including specific recommendations for patients during pregnancy.[17–27]

Major advances have occurred in therapy with the first multicentre randomized clinical trials.[10,11,13–15] Colchicine has been demonstrated as a first-line drug to be added to conventional anti-inflammatory therapies in patients with a first episode of pericarditis or recurrences in order to improve the response to therapy, increase remission rates and reduce recurrences.[10,11,13–15] Specific therapeutic dosing without a loading dose and weight-adjusted doses have been proposed to improve patient compliance.[11,15]

New therapeutic choices have become available for refractory recurrent pericarditis, including alternative immunosuppressive therapies (e.g. azathioprine), intravenous immunoglobulins (IVIGs) and interleukin-1 (IL-1) antagonists (e.g. anakinra).[20–23,28–32] Pericardiectomy has been demonstrated as a possible valuable alternative to additional medical therapies in patients with refractory recurrent pericarditis.[33] The first large prospective and retrospective studies (>100 patients) have investigated the prognosis and complication risk in patients with acute and recurrent pericarditis.[7,9,34–38]

Imaging techniques for the detection of pericardial inflammation [e.g. cardiac magnetic resonance (CMR)] may identify forms of initial reversible constrictive pericarditis, allowing a trial of medical anti-inflammatory therapy that may reduce the need for surgery.[2,39–41]

In conclusion, significant new data have become available since 2004, and a new version of guidelines has become mandatory for clinical practice. Nevertheless, in the field of pericardial diseases there are a limited number of randomized controlled trials (RCTs). Therefore the number of class I level A indications are limited.

2. Epidemiology, aetiology and classification of pericardial diseases

2.1 Epidemiology

Despite the relative high frequency of pericardial diseases, there are few epidemiological data, especially from primary care. Pericarditis is the most common disease of the pericardium encountered in clinical practice. The incidence of acute pericarditis has been reported as 27.7 cases per 100,000 population per year in an Italian urban area.[7] Pericarditis is responsible for 0.1% of all hospital admissions and 5% of emergency room admissions for chest pain.[4,5,42] Data collected from a Finnish national registry (2000–9) showed a standardized incidence rate of hospitalizations for acute pericarditis of 3.32 per 100,000 person-years.[16] These data were limited to hospitalized patients and therefore may account for only a minority of cases, as many patients with pericarditis are commonly not admitted to hospital.[8,9,42,43] Men ages 16–65 years were at higher risk for pericarditis (relative risk 2.02) than women in the general admitted population, with the highest risk difference among young adults compared with the overall population. Acute pericarditis caused 0.20% of all cardiovascular admissions. The proportion of caused admissions declined by an estimated 51% per 10-year increase in age. The in-hospital mortality rate for acute pericarditis was 1.1% and was increased with age and severe co-infections (pneumonia or septicaemia).[16] However, this is a study based on hospital admissions only. Recurrences affect about 30% of patients within 18 months after a first episode of acute pericarditis.[10,11]

2.2 Aetiology

A simple aetiological classification for pericardial diseases is to consider infectious and non-infectious causes (*Table 3*).[4,6,12,44] The aetiology is varied and depends on the epidemiological background, patient population and clinical setting. In developed countries, viruses are usually the most common aetiological agents of pericarditis,[6] whereas tuberculosis (TB) is the most frequent cause of pericardial diseases in the world and developing countries, where TB is endemic. In this setting, TB is often associated with human immunodeficiency virus (HIV) infection, especially in sub-Saharan Africa.[44]

3. Pericardial syndromes

Pericardial syndromes include different clinical presentations of pericardial diseases with distinctive signs and symptoms that can be grouped in specific 'syndromes'. The classical pericardial syndromes include pericarditis, pericardial effusion, cardiac tamponade and constrictive pericarditis. Pericardial effusion and cardiac tamponade may occur without pericarditis and will be considered in separate chapters. Specific considerations apply to cases with pericarditis and concomitant myocardial inflammatory involvement, usually referred to in the literature as 'myopericarditis'.

3.1 Acute pericarditis

Acute pericarditis is an inflammatory pericardial syndrome with or without pericardial effusion.[1–11,42] The clinical diagnosis can be

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Table 3 Aetiology of pericardial diseases. The pericardium may be affected by all categories of diseases, including infectious, autoimmune, neoplastic, iatrogenic, traumatic, and metabolic

A. Infectious causes:
Viral (common): Enteroviruses (coxsackieviruses, echoviruses), herpesviruses (EBV, CMV, HHV-6), adenoviruses, parvovirus B19 (possible overlap with aetiologic viral agents of myocarditis).
Bacterial: *Mycobacterium tuberculosis* (common, other bacterial rare), *Coxiella burnetii*, *Borrelia burgdorferi*, rarely: *Pneumococcus* spp, *Meningococcus* spp, *Gonococcus* spp, *Streptococcus* spp, *Staphylococcus spp*, *Haemophilus* spp, *Chlamydia* spp, *Mycoplasma* spp, *Legionella spp*, *Leptospira* spp, *Listeria* spp, *Providencia stuartii*.
Fungal (very rare): *Histoplasma* spp (more likely in immunocompetent patients), *Aspergillus* spp, *Blastomyces* spp, *Candida* spp (more likely in immunocompromised host).
Parasitic (very rare): *Echinococcus* spp, *Toxoplasma* spp
B. Non-infectious causes:
Autoimmune (common): Systemic autoimmune and auto-inflammatory diseases (systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, scleroderma), systemic vasculitides (i.e. eosinophilic granulomatosis with polyangiitis or allergic granulomatosis, previously named Churg-Strauss syndrome, Horton disease, Takayasu disease, Behçet syndrome), sarcoidosis, familial Mediterranean fever, inflammatory bowel diseases, Still disease.
Neoplastic: Primary tumours (rare, above all pericardial mesothelioma). Secondary metastatic tumours (common, above all lung and breast cancer, lymphoma).
Metabolic: Uraemia, myxoedema, anorexia nervosa, other rare.
Traumatic and Iatrogenic: Early onset (rare): • Direct injury (penetrating thoracic injury, aesophageal perforation). • Indirect injury (non-penetrating thoracic injury, radiation injury). Delayed onset: Pericardial injury syndromes (common) such as postmyocardial infarction syndrome, postpericardiotomy syndrome, posttraumatic, including forms after iatrogenic trauma (e.g. coronary percutaneous intervention, pacemaker lead insertion and radiofrequency ablation).
Drug-related (rare): Lupus-like syndrome (procainamide, hydralazine, methyldopa, isoniazid, phenytoin); antineoplastic drugs (often associated with a cardiomyopathy, may cause a pericardiopathy): doxorubicin, daunorubicin, cytosine arabinoside, 5-fluorouracil, cyclophosphamide; penicillins as hypersensitivity pericarditis with eosinophilia; amiodarone, methysergide, mesalazine, clozapine, minoxidil, dantrolene, practolol, phenylbutazone, thiazides, streptomycin, thiouracils, streptokinase, p-aminosalicylic acid, sulfa-drugs, cyclosporine, bromocriptine, several vaccines, GM-CSF, anti-TNF agents.
Other (common): Amyloidosis, aortic dissection, pulmonary arterial hypertension and chronic heart failure.
Other (uncommon): congenital partial and complete absence of the pericardium.

CMV = cytomegalovirus; EBV = Epstein-Barr virus; GM-CSF = granulocyte-macrophage colonystimulating factor; HHV = human herpesvirus; spp = species; TNF = tumor necrosis factor.

Table 4 Definitions and diagnostic criteria for pericarditis (see text for explanation)

Pericarditis	Definition and diagnostic criteria
Acute	Inflammatory pericardial syndrome to be diagnosed with at least 2 of the 4 following criteria: (1) pericarditic chest pain (2) pericardial rubs (3) new widespread ST-elevation or PR depression on ECG (4) pericardial effusion (new or worsening) Additional supporting findings: - Elevation of markers of inflammation (i.e. C-reactive protein, erythrocyte sedimentation rate, and white blood cell count); - Evidence of pericardial inflammation by an imaging technique (CT, CMR).
Incessant	Pericarditis lasting for >4–6 weeks but <3 months without remission.
Recurrent	Recurrence of pericarditis after a documented first episode of acute pericarditis and a symptom-free interval of 4–6 weeks or longer[a].
Chronic	Pericarditis lasting for >3 months.

CMR = cardiac magnetic resonance; CT = computed tomography; ECG = electrocardiogram.
[a]Usually within 18–24 months but a precise upper limit of time has not been established.

made with two of the following criteria (*Table 4*):[2,4–15] (i) chest pain (>85–90% of cases)—typically sharp and pleuritic, improved by sitting up and leaning forward; (ii) pericardial friction rub (≤33% of cases)—a superficial scratchy or squeaking sound best heard with the diaphragm of the stethoscope over the left sternal border; (iii) electrocardiogram (ECG) changes (up to 60% of cases)—with new widespread ST elevation or PR depression in the acute phase (*Web Figure 1*); and (iv) pericardial effusion (up to 60% of cases, generally mild) (*Web Figure 2*). Additional signs and symptoms may be present according to the underlying aetiology or systemic disease (i.e. signs and symptoms of systemic infection such as fever and leucocytosis, or systemic inflammatory disease or cancer).[45]

Widespread ST-segment elevation has been reported as a typical hallmark sign of acute pericarditis (*Web Figure 1*). However, changes in the ECG imply inflammation of the epicardium, since the parietal pericardium itself is electrically inert.[5–7,34] Typical ECG changes have been reported in up to 60% of cases.[10,11] The temporal evolution of ECG changes with acute pericarditis is highly variable from one patient to another and is affected by therapy. Major differential diagnoses include acute coronary syndromes with ST-segment elevation and early repolarization.[6,12,46]

Elevation of markers of inflammation [i.e. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), as well as elevation of the white blood cell count] is a common and supportive finding in patients with acute pericarditis and may be helpful for monitoring the activity of the disease and efficacy of therapy.[2,47] Patients with concomitant myocarditis may present with an elevation of markers of myocardial injury [i.e. creatine kinase (CK), troponin].[7,34]

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A chest X-ray is generally normal in patients with acute pericarditis since an increased cardiothoracic ratio only occurs with pericardial effusions exceeding 300 ml.[48] In the case of pleuropulmonary diseases, signs of pleuropericardial involvement may be found in patients with pericarditis.[2,3]

Recommendations for diagnosis of acute pericarditis

Recommendations	Class[a]	Level[b]	Ref.[c]
ECG is recommended in all patients with suspected acute pericarditis	I	C	
Transthoracic echocardiography is recommended in all patients with suspected acute pericarditis	I	C	
Chest X-ray is recommended in all patients with suspected acute pericarditis	I	C	
Assessment of markers of inflammation (i.e. CRP) and myocardial injury (i.e. CK, troponin) is recommended in patients with suspected acute pericarditis	I	C	

CK = creatine kinase; CRP = C-reactive protein; ECG = electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

3.1.1 Clinical management and therapy

It is not mandatory to search for the aetiology in all patients, especially in countries with a low prevalence of TB, because of the relatively benign course associated with the common causes of pericarditis and the relatively low yield of diagnostic investigations.[6,8,12,49] Specific final identifiable causes (non-viral–non-idiopathic) as well as high-risk features in the context of acute pericarditis have been identified as being associated with an increased risk of complications during follow-up (tamponade, recurrences and constriction).[9,12,43,50] The major risk factors associated with poor prognosis after multivariate analysis include high fever [>38°C (>100.4°F)], subacute course (symptoms over several days without a clear-cut acute onset), evidence of large pericardial effusion (i.e. diastolic echo-free space >20 mm), cardiac tamponade and failure to respond within 7 days to non-steroidal anti-inflammatory drugs (NSAIDs).[9,43,50] Other risk factors should also be considered (i.e. 'minor risk factors'); these are based on expert opinion and literature review, including pericarditis associated with myocarditis (myopericarditis), immunodepression, trauma and oral anticoagulant therapy.

On this basis a triage for acute pericarditis is proposed (*Figure 1*, *Web Table 6*).[5,6,43] Any clinical presentation that may suggest an underlying aetiology (e.g. a systemic inflammatory disease) or with at least one predictor of poor prognosis (major or minor risk factors) warrants hospital admission and an aetiology search.[9,43,49–51] On the other hand, patients without these features can be managed as outpatients with empiric anti-inflammatories and short-term follow-up after 1 week to assess the response to treatment.[9]

Recommendations for the management of acute pericarditis

Recommendations	Class[a]	Level[b]	Ref.[c]
Hospital admission is recommended for high-risk patients with acute pericarditis (at least one risk factor[d])	I	B	8,9
Outpatient management is recommended for low-risk patients with acute pericarditis	I	B	8,9
Evaluation of response to anti-inflammatory therapy is recommended after 1 week	I	B	8,9

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]See *Figure 1* (both major and minor predictors of poor prognosis).

In patients identified with a cause other than viral infection, specific therapy appropriate to the underlying disorder is indicated[49,51] and the epidemiological background (high vs. low prevalence of TB) should be considered.[8,12,52] The first non-pharmacological recommendation is to restrict physical activity beyond ordinary sedentary life until resolution of symptoms and normalization of CRP for patients not involved in competitive sports.[53] Athletes are recommended to return to competitive sports only after symptoms have resolved and diagnostic tests (i.e. CRP, ECG and echocardiogram) have been normalized.[53,54] A minimal restriction of 3 months (after the initial onset of the attack) has been arbitrarily defined according to expert consensus.[54] We suggest applying this restriction only to athletes, while a shorter period (until remission) may be suitable for non-athletes. Aspirin or NSAIDs are mainstays of therapy for acute pericarditis.[5,6,55,56] Different anti-inflammatory drugs have been proposed (*Table 5*).

The choice of drug should be based on the history of the patient (contraindications, previous efficacy or side effects), the presence of concomitant diseases (favouring aspirin over other NSAIDs when aspirin is already needed as antiplatelet treatment) and physician expertise.[56]

Colchicine is recommended at low, weight-adjusted doses to improve the response to medical therapy and prevent recurrences.[10,11,57–59] Tapering of colchicine is not mandatory but may be considered to prevent persistence of symptoms and recurrence.[5,6,56] Corticosteroids should be considered as a second option in patients with contraindications and failure of aspirin or NSAIDs because of the risk of favouring the chronic evolution of the disease and promoting drug dependence; in this case

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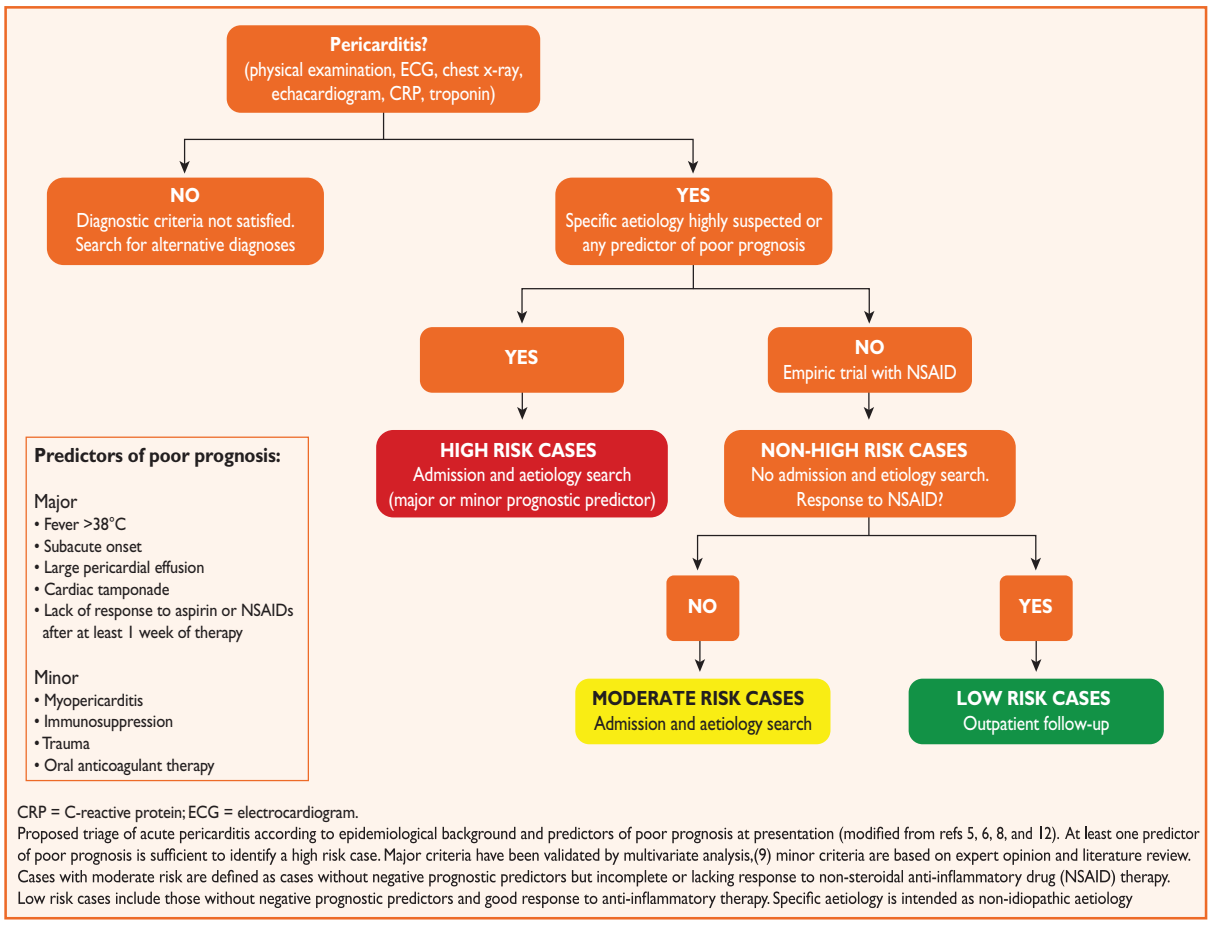

CRP = C-reactive protein; ECG = electrocardiogram.
Proposed triage of acute pericarditis according to epidemiological background and predictors of poor prognosis at presentation (modified from refs 5, 6, 8, and 12). At least one predictor of poor prognosis is sufficient to identify a high risk case. Major criteria have been validated by multivariate analysis,(9) minor criteria are based on expert opinion and literature review. Cases with moderate risk are defined as cases without negative prognostic predictors but incomplete or lacking response to non-steroidal anti-inflammatory drug (NSAID) therapy. Low risk cases include those without negative prognostic predictors and good response to anti-inflammatory therapy. Specific aetiology is intended as non-idiopathic aetiology

Figure 1 Proposed triage of pericarditis.

Table 5 Commonly prescribed anti-inflammatory therapy for acute pericarditis

Drug	Usual dosing[a]	Tx duration[b]	Tapering[a]
Aspirin	750–1000 mg every 8h	1–2 weeks	Decrease doses by 250–500 mg every 1–2 weeks
Ibuprofen	600 mg every 8h	1–2 weeks	Decrease doses by 200–400 mg every 1–2 weeks
Colchicine	0.5 mg once (<70 kg) or 0.5 mg b.i.d. (≥70 kg)	3 months	Not mandatory, alternatively 0.5 mg every other day (< 70 kg) or 0.5 mg once (≥70 kg) in the last weeks

b.i.d. = twice daily; CRP = C-reactive protein; NSAIDs = non-steroidal anti-inflammatory drugs; Tx = treatment.
[a]Tapering should be considered for aspirin and NSAIDs.
[b]Tx duration is symptoms and CRP guided but generally 1–2 weeks for uncomplicated cases. Gastroprotection should be provided. Colchicine is added on top of aspirin or ibuprofen.

they are used with colchicine. If used, low to moderate doses (i.e. prednisone 0.2–0.5 mg/kg/day or equivalent) should be recommended instead of high doses (i.e. prednisone 1.0 mg/kg/day or equivalent).[35] The initial dose should be maintained until resolution of symptoms and normalization of CRP, then tapering should be considered.[5,6,35,47,56]

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Recommendations for the treatment of acute pericarditis

Recommendations	Class[a]	Level[b]	Ref.[c]
Aspirin or NSAIDs are recommended as first-line therapy for acute pericarditis with gastroprotection	I	A	55
Colchicine is recommended as first-line therapy for acute pericarditis as an adjunct to aspirin/NSAID therapy	I	A	10,11, 58,59
Serum CRP should be considered to guide the treatment length and assess the response to therapy	IIa	C	
Low-dose corticosteroids[d] should be considered for acute pericarditis in cases of contraindication/failure of aspirin/ NSAIDs and colchicine, and when an infectious cause has been excluded, or when there is a specific indication such as autoimmune disease	IIa	C	
Exercise restriction should be considered for non-athletes with acute pericarditis until resolution of symptoms and normalization of CRP, ECG and echocardiogram	IIa	C	
For athletes, the duration of exercise restriction should be considered until resolution of symptoms and normalization of CRP, ECG and echocardiogram—at least 3 months is recommended	IIa	C	
Corticosteroids are not recommended as first-line therapy for acute pericarditis	III	C	

CRP = C-reactive protein; ECG = electrocardiogram; NSAIDs = non-steroidal anti-inflammatory drugs.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Added to colchicine.

3.1.2 Prognosis

Most patients with acute pericarditis (generally those with presumed viral or idiopathic pericarditis) have a good long-term prognosis.[36] 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 <1% of patients with acute idiopathic pericarditis, and is also more common in patients with a specific aetiology. The risk of developing constriction can be classified as low (<1%) for idiopathic and presumed viral pericarditis; intermediate (2–5%) for autoimmune, immune-mediated and neoplastic aetiologies; and high (20–30%) for bacterial aetiologies, especially with TB and purulent pericarditis.[36] Approximately 15–30% of patients with idiopathic acute pericarditis who are not treated with colchicine will develop either recurrent or incessant disease, while colchicine may halve the recurrence rate.[10,11,13–15]

3.2 Incessant and chronic pericarditis

The term 'incessant' has been adopted for cases with persistent symptoms without a clear-cut remission after the acute episode. The term 'chronic' generally refers—especially for pericardial effusions—to disease processes lasting >3 months.[48] The Task Force suggests that the term 'acute' should be adopted for new-onset pericarditis, 'incessant' for pericarditis with symptoms persisting for >4–6 weeks (that is generally the approximate length of conventional anti-inflammatory therapy and its tapering),[11,60] and 'chronic' for pericarditis lasting >3 months.

3.3 Recurrent pericarditis

Recurrent pericarditis is diagnosed with a documented first episode of acute pericarditis, a symptom-free interval of 4–6 weeks or longer and evidence of subsequent recurrence of pericarditis (*Table 4*).[11,13–15] Diagnosis of recurrence is established according to the same criteria as those used for acute pericarditis. CRP,[2,47] computed tomography (CT) and/or CMR may provide confirmatory findings to support the diagnosis in atypical or doubtful cases showing pericardial inflammation through evidence of oedema and contrast enhancement of the pericardium.[2,39]

The recurrence rate after an initial episode of pericarditis ranges from 15 to 30%,[10,11] and may increase to 50% after a first recurrence in patients not treated with colchicine,[13–15] particularly if treated with corticosteroids.

In developed countries, the aetiology is often not identified in most immunocompetent patients, and it is generally presumed to be immune-mediated.[60–62] A common cause of recurrence is inadequate treatment of the first episode of pericarditis. In up to 20% of cases, when additional virological studies have been conducted on pericardial fluid and tissue, a viral aetiology is detected.[63]

3.3.1 Therapy

Recurrent pericarditis therapy should be targeted at the underlying aetiology in patients with an identified cause. Aspirin or NSAIDs remain the mainstay of therapy (*Table 6*, *Web Box*, *Web Table 1A*). Colchicine is recommended on top of standard anti-inflammatory therapy, without a loading dose and using weight-adjusted doses (i.e. 0.5 mg once daily if body weight is <70 kg or 0.5 mg twice daily if it is ≥70 kg, for ≥6 months) (*Table 6*, *Web Table 1B*) in order to improve the response to medical therapy, improve remission rates and prevent recurrences.[13–15,58,59]

In cases of incomplete response to aspirin/NSAIDs and colchicine, corticosteroids may be used, but they should be added at low to moderate doses to aspirin/NSAIDs and colchicine as triple therapy, not replace these drugs, in order to achieve better control of symptoms. Corticosteroids at low to moderate doses (i.e. prednisone 0.2–0.5 mg/kg/day) should be avoided if infections, particularly bacterial and TB, cannot be excluded and should be restricted to patients with specific indications (i.e. systemic inflammatory diseases, post-pericardiotomy syndromes, pregnancy) or NSAID contraindications (true allergy, recent peptic ulcer or gastrointestinal bleeding, oral anticoagulant therapy when the bleeding risk is considered high or unacceptable) or intolerance or persistent disease despite appropriate doses.[58] Although corticosteroids provide rapid control of symptoms, they favour

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Table 6 Commonly prescribed anti-inflammatory therapies for recurrent pericarditis (for further details see Web Tables 1A and 1B)

Drug	Usual initial dose[a]	Tx duration[b]	Tapering[a]
Aspirin	500–1000 mg every 6–8 hours (range 1,5–4 g/day)	weeks-months	Decrease doses by 250–500 mg every 1–2 weeks[b]
Ibuprofen	600 mg every 8 hours (range 1200–2400 mg)	weeks-months	Decrease doses by 200–400 mg every 1–2 weeks[b]
Indomethacin	25–50 mg every 8 hours: start at lower end of dosing range and titrate upward to avoid headache and dizziness.	weeks-months	Decrease doses by 25 mg every 1–2 weeks[b]
Colchicine	0.5 mg twice or 0.5 mg daily for patients <70 kg or intolerant to higher doses.	At least 6 months	Not necessary, alternatively 0.5 mg every other day (<70 kg) or 0.5 mg once (≥70 kg) in the last weeks

Tx = treatment.
[a]Tapering should be considered for aspirin and NSAIDs.
[b]Longer tapering times for more difficult, resistant cases may be considered.

chronicity, more recurrences and side effects.[35,55,61] If corticosteroids are used, their tapering should be particularly slow. A critical threshold for recurrences is a 10–15 mg/day dose of prednisone or equivalent. At this threshold, very slow decrements as small as 1.0–2.5 mg at intervals of 2–6 weeks are useful. In cases of recurrence, every effort should be made not to increase the dose or to reinstate corticosteroids (*Tables 6* and *7*).[5,6,35,61]

After obtaining a complete response, tapering should be done with a single class of drug at a time before colchicine is gradually discontinued (over several months in the most difficult cases). Recurrences are possible after discontinuation of each drug. Each tapering should be attempted only if symptoms are absent and CRP is normal.[5,6,47,56] The Task Force does not recommend influenza vaccine as a preventive measure for pericarditis in patients with recurrent pericarditis, since the influenza virus is not a usual cause of pericarditis. The influenza vaccine should be administered according to specific indications beyond pericarditis; moreover, recurrences are generally immune mediated, and inappropriate or unwanted stimulation of the immune system may trigger or worsen an episode of pericarditis.

An alternative effective approach to minimize systemic side effects related to corticosteroids may be intrapericardial administration of non-absorbable corticosteroids,[64,65] but this technique requires further investigation. For those patients who require unacceptably high long-term doses of corticosteroids (e.g. prednisone 15–25 mg/day) or who do not respond to anti-inflammatory therapies, several drugs have been used, including azathioprine,[28] IVIG (immunomodulatory but also anti-viral)[29,30] and anakinra, a recombinant IL-1β receptor antagonist,[31,32] but strong evidence-based data are lacking (*Web Table 2*). Other immunosuppressive drugs [i.e. cyclophosphamide, cyclosporine, methotrexate, hydroxychloroquine, anti-tumour necrosis factor (TNF) agents] have been only anecdotally reported. Less toxic agents might be preferred, and eventually combined, with the therapy being tailored to the individual patient and physician experience (*Figure 2*). Azathioprine is mainly a slow-acting corticosteroid-sparing agent, useful to control the disease for a long-term follow-up, while anakinra and IVIG are effective during the acute phase, though recurrences may occur after discontinuation.[29–32] Drugs such as IVIG, anakinra and azathioprine may be considered in cases of proven infection-negative, corticosteroid-dependent, recurrent pericarditis not responsive to colchicine after careful assessment of the costs, risks and eventually consultation by multidisciplinary experts, including immunologists and/or rheumatologists, in the absence of a specific expertise. It is also mandatory to educate the patient and his/her caregivers about the clinical risks related to immunomodulatory/immunosuppressive drugs and the safety measures to adopt during the treatment. As a last resort, pericardiectomy may be considered, but only after a thorough trial of unsuccessful medical therapy, and with referral of the patient to a centre with specific expertise in this surgery.[33] The physical activity restrictions in acute pericarditis apply also to recurrences.[53,54]

Table 7 Tapering of corticosteroids[35] (dosage information is provided for prednisone)

Starting dose 0.25–0.50 mg/kg/day[a]	Tapering[b]
>50 mg	10 mg/day every 1–2 weeks
50–25 mg	5–10 mg/day every 1–2 weeks
25–15 mg	2.5 mg/day every 2–4 weeks
<15 mg	1.25–2.5 mg/day every 2–6 weeks

[a]Avoid higher doses except for special cases, and only for a few days, with rapid tapering to 25 mg/day. Prednisone 25 mg are equivalent to methylprednisolone 20 mg.
[b]Every decrease in prednisone dose should be done only if the patient is asymptomatic and C-reactive protein is normal, particularly for doses <25 mg/day. 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.

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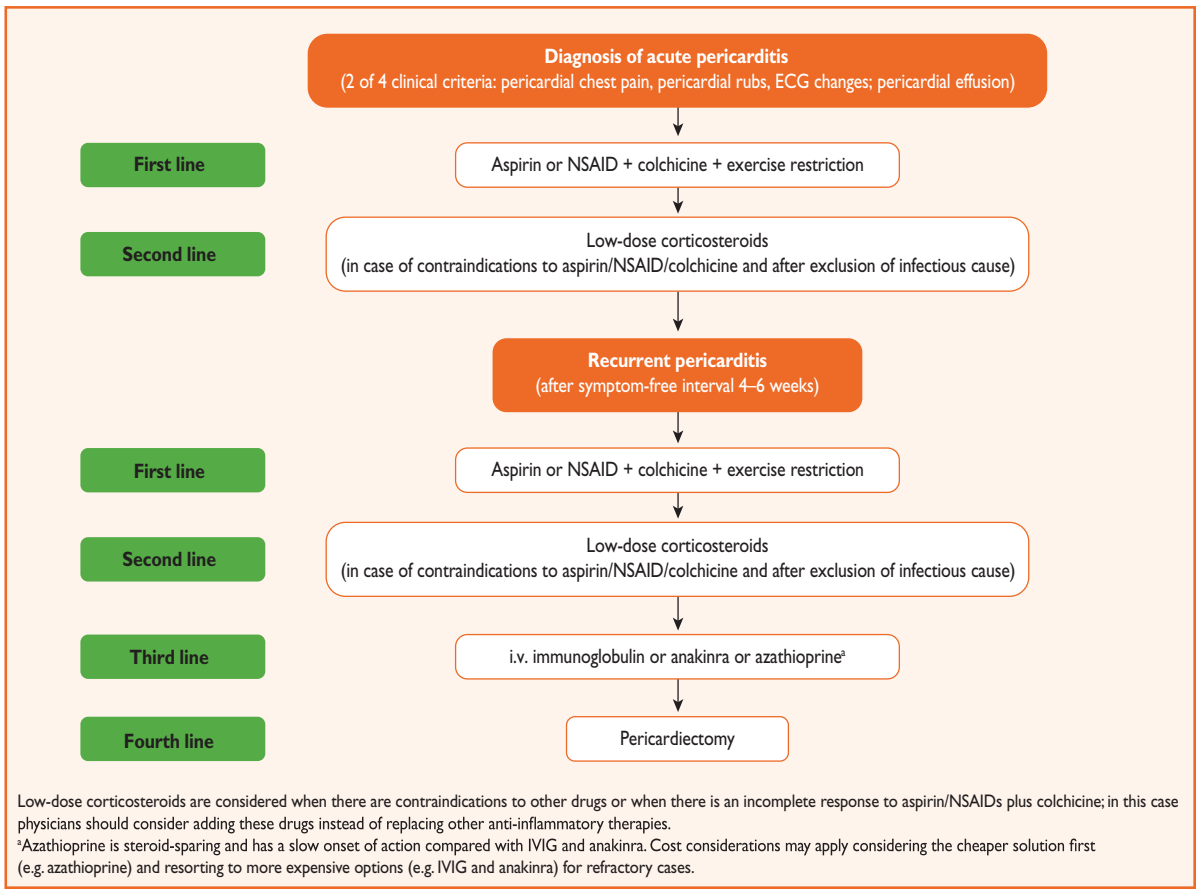

Figure 2 Therapeutic algorithm for acute and recurrent pericarditis (see text for explanation).

Recommendations for the management of recurrent pericarditis

Recommendations	Class[a]	Level[b]	Ref.[c]
Aspirin and NSAIDs are mainstays of treatment and are recommended at full doses, if tolerated, until complete symptom resolution	I	A	55,56
Colchicine (0.5 mg twice daily or 0.5 mg daily for patients <70 kg or intolerant to higher doses); use for 6 months is recommended as an adjunct to aspirin/NSAIDs	I	A	13–15, 58,59
Colchicine therapy of longer duration (>6 months) should be considered in some cases, according to clinical response	IIa	C	
CRP dosage should be considered to guide the treatment duration and assess the response to therapy	IIa	C	
After CRP normalization, a gradual tapering of therapies should be considered, tailored to symptoms and CRP, stopping a single class of drugs at a time	IIa	C	
Drugs such as IVIG, anakinra and azathioprine may be considered in cases of corticosteroid-dependent recurrent pericarditis in patients not responsive to colchicine	IIb	C	
Exercise restriction should be considered for non-athletes with recurrent pericarditis until symptom resolution and CRP normalization, taking into account the previous history and clinical conditions	IIa	C	
Exercise restriction for a minimum of 3 months should be considered for athletes with recurrent pericarditis until symptom resolution and normalization of CRP, ECG and echocardiogram	IIa	C	

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If ischaemic heart disease is a concern or antiplatelet therapy is required, aspirin should be considered, at medium high doses (1–2.4 g/day)* (*Web box*)	IIa	C	
If symptoms recur during therapy tapering, the management should consider not increasing the dose of corticosteroids to control symptoms, but increasing to the maximum dose of aspirin or NSAIDs, well distributed, generally every 8 hours, and intravenously if necessary, adding colchicine and adding analgesics for pain control	IIa	C	
Corticosteroid therapy is not recommended as a first line-approach	III	B	13–15, 35,37, 55

CRP = C-reactive protein; ECG = electrocardiogram; IVIG = intravenous immunoglobulin; NSAIDs = non-steroidal anti-inflammatory drugs.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

3.3.2 Prognosis

Severe complications are uncommon in idiopathic recurrent pericarditis.[37,60,61] Cardiac tamponade is rare and generally occurs at the beginning of the disease. Constrictive pericarditis has never been reported in these patients, despite numerous recurrences, and the overall risk is lower than that recorded after a first episode of acute pericarditis (<1%).[36,37,61] Thus it is important to reassure patients about their prognosis, explaining the nature of the disease and its likely course. The complication rates are related to the aetiology and not to the number of recurrences. Drug treatment should take into account this favourable outcome to avoid more toxic agents. However, quality of life can be severely affected in patients with repeated recurrences, subacute or incessant pericarditis and glucocorticoid dependence.

3.4 Pericarditis associated with myocardial involvement (myopericarditis)

Pericarditis and myocarditis share common aetiologies, and overlapping forms may be encountered in clinical practice.[34,66] Pericarditis with known or clinically suspected concomitant myocardial involvement should be referred to as 'myopericarditis', while predominant myocarditis with pericardial involvement should be referred to as 'perimyocarditis', according to Task Force consensus. The classical presentation is chest pain associated with other signs of pericarditis (pericardial rubs, ST-segment elevation and pericardial effusion) plus the elevation of markers of myocardial damage (i.e. troponins). Limited clinical data on the causes of myopericarditis suggest that viral infections are among the most common causes in developed countries, while other infectious causes are more common in developing countries (especially TB). Cardiotropic viruses can cause pericardial and myocardial inflammation via direct cytolytic or cytotoxic effects and/or subsequent immune-mediated mechanisms. Such mechanisms are especially involved in cases associated with connective tissue diseases, inflammatory bowel diseases and radiation-induced, drug-induced or vaccinia-associated myopericardial involvement. Many cases of myopericarditis are subclinical. In other patients, cardiac symptoms and signs are masked by pronounced systemic manifestations of infection or inflammation.[66] In many cases, myopericarditis manifestations are preceded by or are sometimes concomitant with an acute respiratory illness (especially acute tonsillitis, pneumonia) or gastroenteritis. The increased sensitivity of troponin assays and contemporary widespread use of troponins has greatly increased the reported number of cases.[7,34,66–68]

3.4.1 Definition and diagnosis

The diagnosis of predominant pericarditis with myocardial involvement, or 'myopericarditis', can be clinically established if patients with definite criteria for acute pericarditis show elevated biomarkers of myocardial injury (troponin I or T, CK-MB fraction) without newly developed focal or diffuse impairment of left ventricular function in echocardiography or CMR.[34] The term myopericarditis indicates a primarily pericarditic syndrome with minor myocardial involvement, which describes the majority of combined pericarditis and myocarditis cases encountered in clinical practice.[7,9,34,68]

On the other hand, evidence of new-onset focal or diffuse reduction of left ventricular function in patients with elevated myocardial biomarkers and clinical criteria for acute pericarditis suggests predominant myocarditis with pericardial involvement ('perimyocarditis').[34,66] Definite confirmation of the presence of myocarditis will require endomyocardial biopsy according to the Myocardial and Pericardial Diseases Working Group position statement.[69] However, the benign prognosis of patients with suspected concomitant myocardial involvement in predominant pericarditis (myopericarditis), with absent or mild left ventricular dysfunction, and no symptoms of heart failure does not clinically require endomyocardial biopsy.[6,34,66–68,70,71]

In cases of pericarditis with suspected associated myocarditis, coronary angiography (according to clinical presentation and risk factor assessment) is recommended in order to rule out acute coronary syndromes. CMR is recommended for the confirmation of myocardial involvement and to rule out ischaemic myocardial necrosis in the absence of significant coronary disease; this has clinical and therapeutic implications.[34,66]

3.4.2 Management

Hospitalization is recommended for diagnosis and monitoring of patients with myocardial involvement and differential diagnosis, especially with acute coronary syndromes. In the setting of myopericarditis, management is similar to that recommended for pericarditis. Empirical anti-inflammatory therapies (i.e. aspirin 1500–3000 mg/day) or NSAIDs (ibuprofen 1200–2400 mg/day or indomethacin 75–150 mg/day) are usually prescribed to control chest pain, while corticosteroids are prescribed as a second choice in cases of contraindication, intolerance or failure of aspirin/NSAIDs.[66] In the setting of myopericarditis, some authors recommend reducing dosages, as compared with pure pericarditis, because in animal models of myocarditis, NSAIDs have been shown to be non-efficacious and may enhance inflammation, increasing mortality.[69,70,72,73]

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However, the application of these findings from animal models to humans may be questionable.[66] In addition, there are insufficient data to recommend the use of colchicine, which is a well-established adjunctive treatment for acute and recurrent pericarditis.[58] Despite the lack of specific therapies for most cases, several non-specific recommendations are important. Rest and avoidance of physical activity beyond normal sedentary activities is recommended in all patients with myopericarditis.[53,54,66]

Sudden cardiac death cases have been reported in military personnel after strenuous exertion and also in male athletes without prodromic symptoms [football (soccer) players, swimming].[53,54,66] While in isolated pericarditis, return to exercise is permissible when there is no further evidence of active disease in non-athletes, or after 3 months in athletes, the presence or suspicion of myocardial involvement leads to contraindication of physical exercise for at least 6 months from the onset of the illness according to expert opinion and previous recommendations for participation in competitive sports.[53,54,66]

3.4.3 Prognosis

Myocardial involvement in pericarditis has a good prognosis, and several observational series have demonstrated no evolution to heart failure or mortality in patients with myopericarditis.[34,66–68,70,71]

Recommendations for the diagnosis and management of pericarditis associated with myocarditis

Recommendations	Class[a]	Level[b]	Ref.[c]
In cases of pericarditis with suspected associated myocarditis, coronary angiography (according to clinical presentation and risk factor assessment) is recommended in order to rule out acute coronary syndromes	I	C	
Cardiac magnetic resonance is recommended for the confirmation of myocardial involvement	I	C	
Hospitalization is recommended for diagnosis and monitoring in patients with myocardial involvement	I	C	
Rest and avoidance of physical activity beyond normal sedentary activities is recommended in non-athletes and athletes with myopericarditis for a period of 6 months	I	C	
Empirical anti-inflammatory therapies (lowest efficacious doses) should be considered to control chest pain	IIa	C	

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

3.5 Pericardial effusion

The normal pericardial sac contains 10–50 ml of pericardial fluid as a plasma ultrafiltrate that acts as a lubricant between the pericardial layers. Any pathological process usually causes an inflammation with the possibility of increased production of pericardial fluid (exudate). An alternative mechanism of accumulation of pericardial fluid may be decreased reabsorption due to a general increase in systemic venous pressure as a result of congestive heart failure or pulmonary hypertension (transudate).[48] Pericardial effusion may be classified according to its onset (acute or subacute vs. chronic when lasting >3 months), distribution (circumferential or loculated), haemodynamic impact (none, cardiac tamponade, effusive-constrictive), composition (exudate, transudate, blood, rarely air, or gas from bacterial infections) and, in particular, by its size (*Table 8*) based on a simple semiquantitative echocardiographic assessment as mild (<10 mm), moderate (10–20 mm) or large (>20 mm) (*Web Figure 2*).[48] This semiquantitative assessment has also proven to be useful in estimating the risk of specific aetiology and complications during follow-up in the setting of pericarditis.[9,48,51] In the last 20 years, five major surveys have been published on the characteristics of moderate to large pericardial effusions (*Web Table 3*).[74–78]

Table 8 Classification of pericardial effusion

Onset	Acute Subacute Chronic (>3 months)
Size	Mild <10 mm Moderate 10–20mm Large >20 mm
Distribution	Circumferential Loculated
Composition	Transudate Exudate

A significant proportion of patients with pericardial effusion are asymptomatic and pericardial effusion constitutes an incidental and unexpected finding on X-ray or echocardiogram performed for other reasons. According to these series, many cases remain idiopathic in developed countries (up to 50%), while other common causes include cancer (10–25%), infections (15–30%), iatrogenic causes (15–20%) and connective tissue diseases (5–15%), whereas TB is the dominant cause in developing countries (>60%), where TB is endemic.[52,79] In the setting of pericarditis with pericardial effusion, the prevalence of malignant or infectious aetiologies ranges from 15 to 50% depending on the published series.[6,9]

3.5.1 Clinical presentation and diagnosis

The clinical presentation of pericardial effusion varies according to the speed of pericardial fluid accumulation. If pericardial fluid is rapidly accumulating, such as after wounds or iatrogenic perforations, the evolution is dramatic and even small amounts of blood may cause an increase in intrapericardial pressure within minutes and overt cardiac tamponade. On the other hand, a slow accumulation of pericardial fluid allows the collection of a large effusion in days to weeks before a significant increase in pericardial pressure causes symptoms and signs (*Web Figure 3*).[48,80,81]

Classic symptoms include dyspnoea on exertion progressing to orthopnoea, chest pain and/or fullness. Additional occasional

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symptoms due to local compression may include nausea (diaphragm), dysphagia (oesophagus), hoarseness (recurrent laryngeal nerve) and hiccups (phrenic nerve). Non-specific symptoms include cough, weakness, fatigue, anorexia and palpitations, and reflect the compressive effect of the pericardial fluid on contiguous anatomic structures or reduced blood pressure and secondary sinus tachycardia.[82–84] Fever is a non-specific sign that may be associated with pericarditis, either infectious or immune mediated (i.e. systemic inflammatory diseases).[45]

Physical examination may be absolutely normal in patients without haemodynamic compromise. When tamponade develops, classic signs include neck vein distension with elevated jugular venous pressure at bedside examination, pulsus paradoxus and diminished heart sounds on cardiac auscultation in cases of moderate to large effusions.[82–84] Pericardial friction rubs are rarely heard; they can usually be detected in patients with concomitant pericarditis.[8]

The diagnosis of pericardial effusion is generally performed by echocardiography, which also enables semiquantitative assessment of the pericardial effusion size and its haemodynamic effects. Although echocardiography remains the primary diagnostic tool for the study of pericardial diseases because of its widespread availability, portability and limited costs, CT and CMR provide a larger field of view, allowing the detection of loculated pericardial effusion and pericardial thickening and masses, as well as associated chest abnormalities.[2,3,84]

Recommendations for the diagnosis of pericardial effusion

Recommendations	Class[a]	Level[b]	Ref.[c]
Transthoracic echocardiography is recommended in all patients with suspected pericardial effusion	I	C	
Chest X-ray is recommended in patients with a suspicion of pericardial effusion or pleuropulmonary involvement	I	C	
Assessment of markers of inflammation (i.e. CRP) are recommended in patients with pericardial effusion	I	C	
CT or CMR should be considered in suspected cases of loculated pericardial effusion, pericardial thickening and masses, as well as associated chest abnormalities	IIa	C	

CMR = cardiac magnetic resonance; CRP = C-reactive protein; CT = computed tomography.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

3.5.2 Triage and management

When a pericardial effusion is detected, the first step is to assess its size, haemodynamic importance (especially the presence of cardiac tamponade) and possible associated diseases (either cardiovascular or systemic diseases). Pericardial effusion is often associated with known or unknown (e.g. hypothyroidism) medical conditions (up to 60% of cases).[48,75,82] If inflammatory signs are present, the clinical management should be that of pericarditis. Cardiac tamponade without inflammatory signs is associated with a higher risk of a neoplastic aetiology (likelihood ratio 2.9), whereas a severe effusion without cardiac tamponade and inflammatory signs is usually associated with a chronic idiopathic aetiology (likelihood ratio 20).[75] A practical routine evaluation for triage of pericardial effusion is presented in *Figure 3*.[48,82]

Recommendations for the initial management of pericardial effusion

Recommendations	Class[a]	Level[b]	Ref.[c]
Admission is recommended for high-risk patients with pericardial effusion[d]	I	C	
A triage of patients with pericardial effusion is recommended as in *Figure 3*	I	C	

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Similar risk criteria as for pericarditis (see *Figure 1*).

In chronic effusion with no definite aetiology, there are no data on non-steroidal anti-inflammatory drugs (NSAIDs), colchicine and corticosteroids. If markers of inflammation are elevated, a trial of NSAIDs and/or colchicine and/or low-dose corticosteroids may be tried.

3.5.3 Therapy

Therapy of pericardial effusion should be targeted at the aetiology as much as possible. In about 60% of cases, the effusion is associated with a known disease and the essential treatment is that of the underlying disease.[48,75,82] When pericardial effusion is associated with pericarditis, management should follow that of pericarditis. When a pericardial effusion becomes symptomatic without evidence of inflammation or when empiric anti-inflammatory drugs are not successful, drainage of the effusion should be considered. Pericardiocentesis with prolonged pericardial drainage of up to 30 ml/24 h may be considered in order to promote adherence of pericardial layers and prevent further accumulation of fluid; however, evidence to support this indication is based on case reports, retrospective studies and expert opinion.[48,82,84]

Unfortunately, there are no proven effective medical therapies to reduce an isolated effusion. In the absence of inflammation, NSAIDs, colchicine and corticosteroids are generally not effective.[82,85] Pericardiocentesis alone may be necessary for the resolution of large effusions, but recurrences are also common, and pericardiectomy or less invasive options (i.e. pericardial window) should be considered whenever fluid reaccumulates, becomes loculated or biopsy material is required.[48]

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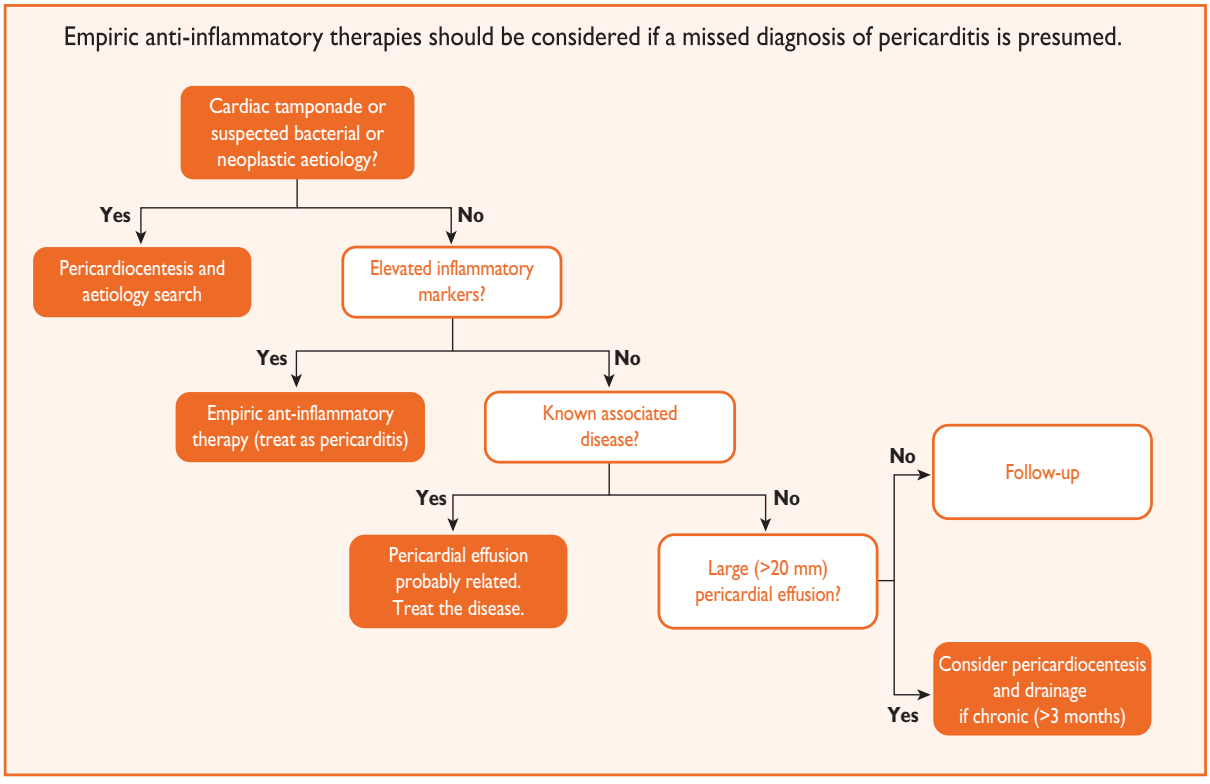

Figure 3 A simplified algorithm for pericardial effusion triage and management.

Recommendations for the therapy of pericardial effusion

Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended to target the therapy of pericardial effusion at the aetiology	I	C	
Aspirin/NSAIDs/colchicine and treatment of pericarditis is recommended when pericardial effusion is associated with systemic inflammation	I	C	
Pericardiocentesis or cardiac surgery is indicated for cardiac tamponade or for symptomatic moderate to large pericardial effusions not responsive to medical therapy, and for suspicion of unknown bacterial or neoplastic aetiology	I	C	

NSAIDs = non-steroidal anti-inflammatory drugs.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

3.5.4 Prognosis and follow-up

The prognosis of pericardial effusion is essentially related to the aetiology.[48,82,86] The size of the effusion is correlated with the prognosis, as moderate to large effusions are more common for specific aetiologies such as bacterial and neoplastic conditions.[9,48] Idiopathic pericardial effusion and pericarditis have an overall good prognosis with a very low risk of complications, especially if the effusion is mild to moderate. In contrast with these observations, a recently published prospective study has shown that even with mild pericardial effusion the overall prognosis may be worse than in age- and sex-matched controls.[87]

Large idiopathic chronic effusions (>3 months) have a 30–35% risk of progression to cardiac tamponade.[88] Also, subacute (4–6 weeks) large effusions not responsive to conventional therapy and with echocardiographic signs of collapse of the right chambers may have an increased risk of progression according to some authors, who recommend preventive drainage in such cases.[89] Documented idiopathic pericarditis has a very low risk of constrictive pericarditis despite several recurrences: here the risk is related to the aetiology and not the number of recurrences.[36] The follow-up of pericardial effusion is mainly based on the evaluation of symptoms and the echocardiographic size of the effusion, as well as additional features such as inflammatory markers (i.e. CRP).[48]

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A mild idiopathic effusion (<10 mm) is usually asymptomatic, generally has a good prognosis and does not require specific monitoring.[48] Moderate to large effusions (>10 mm) may worsen, and especially severe effusions may evolve towards cardiac tamponade in up to one-third of cases. For idiopathic moderate effusions, an appropriate timing for echocardiographic follow-up may be an echocardiogram every 6 months. For a severe effusion, an echocardiographic follow-up may be every 3–6 months. A tailored follow-up is also warranted considering the relative stability or evolution of the size.[48] Specific considerations on pericardial effusion in the post-operative setting are discussed in the section on post-cardiac injury syndromes (section 5.5).

3.6 Cardiac tamponade

Cardiac tamponade is a life-threatening, slow or rapid compression of the heart due to the pericardial accumulation of fluid, pus, blood, clots or gas as a result of inflammation, trauma, rupture of the heart or aortic dissection.[81,84] Clinical signs in a patient with cardiac tamponade include tachycardia, hypotension, pulsus paradoxus, raised jugular venous pressure, muffled heart sounds, decreased electrocardiographic voltage with electrical alternans and an enlarged cardiac silhouette on chest X-ray with slow-accumulating effusions.[81–84] A key diagnostic finding is pulsus paradoxus (conventionally defined as an inspiratory decrease in systolic arterial pressure of >10 mmHg during normal breathing). Pulsus paradoxus is due to exaggerated ventricular interdependence occurring in cardiac tamponade, when the overall volume of cardiac chambers becomes fixed and any change in the volume of one side of the heart causes the opposite changes in the other side (i.e. inspiratory increase of venous return and right chambers with decreased volume of left chambers and reduced systemic blood pressure). The magnitude of clinical and haemodynamic abnormalities depends on the rate of accumulation and amount of pericardial contents, the distensibility of the pericardium and the filling pressures and compliance of the cardiac chambers (*Web Figure 3*). Various causes for cardiac tamponade are listed in *Table 9*.

The stiffness of the pericardium determines fluid increments precipitating tamponade, as illustrated by characteristic pericardial pressure–volume (strain–stress) curves: there is an initial slow ascent, followed by an almost vertical rise (*Web Figure 3*). This steep rise makes tamponade a 'last-drop' phenomenon: the final increment produces critical cardiac compression and the first decrement during drainage produces the largest relative decompression.[80–84]

In a patient with clinical suspicion of cardiac tamponade, several diagnostic tools are required. An ECG may show signs of pericarditis, with especially low QRS voltages and electrical alternans. Both ECG signs are generally considered to be an expression of the damping effect of pericardial fluid and swinging heart. Echocardiography is the single most useful diagnostic tool to identify pericardial effusion and estimate its size, location and degree of haemodynamic impact. Also, echocardiography is used to guide pericardiocentesis with excellent safety and efficacy. Signs of tamponade can be identified by echocardiography: swinging of the heart, early diastolic collapse of the right ventricle, late diastolic collapse of the right atrium, abnormal ventricular septal motion, exaggerated respiratory variability (>25%) in mitral inflow velocity, inspiratory decrease and expiratory increase in pulmonary vein diastolic forward flow, respiratory variation in ventricular chamber size, aortic outflow velocity (echocardiographic pulsus paradoxus) and inferior vena cava plethora.[2,3,82,84] CT and CMR are often less readily available and are generally unnecessary unless Doppler echocardiography is not feasible. Cardiac catheterization is rarely used to diagnose cardiac tamponade. It will show equilibration of average diastolic pressure and characteristic respiratory reciprocation of cardiac pressures, i.e. an inspiratory increase on the right and a concomitant decrease on the left—the proximate cause of pulsus paradoxus. Except in low-pressure tamponade, diastolic pressures throughout the heart are usually in the range of 15–30 mmHg.

The treatment of cardiac tamponade involves drainage of the pericardial fluid, preferably by needle pericardiocentesis, with the use of echocardiographic or fluoroscopic guidance, and should be performed without delay in unstable patients. Alternatively, drainage is performed by a surgical approach, especially in some situations such as purulent pericarditis or in urgent situations with bleeding into the pericardium. A triage system (*Web Figure 4*) has been proposed by the ESC Working Group on Myocardial and Pericardial Diseases in order to guide the timing of the intervention and the possibility of transferring the patient to a referral centre.[84] This triage system is essentially based on expert consensus and requires additional validation in order to be recommended in clinical practice.

Table 9 Causes of cardiac tamponade

Common causes: • Pericarditis • Tuberculosis • Iatrogenic (invasive procedure-related, post-cardiac surgery) • Trauma • Neoplasm/malignancy
Uncommon causes: • Collagen vascular diseases (systemic lupus erythematosus, rheumatoid arthritis, scleroderma) • Radiation induced • Postmyocardial infarction • Uraemia • Aortic dissection • Bacterial infection • Pneumopericardium

Recommendations for the diagnosis and treatment of cardiac tamponade

Recommendations	Class[a]	Level[b]	Ref.[c]
In a patient with clinical suspicion of cardiac tamponade, echocardiography is recommended as the first imaging technique to evaluate the size, location and degree of haemodynamic impact of the pericardial effusion	I	C	
Urgent pericardiocentesis or cardiac surgery is recommended to treat cardiac tamponade	I	C	

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A judicious clinical evaluation including echocardiographic findings is recommended to guide the timing of pericardiocentesis	I	C	
A triage system may be considered to guide the timing of pericardiocentesis (*Web Figure 4*)	IIb	C	
Vasodilators and diuretics are not recommended in the presence of cardiac tamponade	III	C	

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

3.7 Constrictive pericarditis

Constrictive pericarditis can occur after virtually any pericardial disease process, but only rarely follows recurrent pericarditis.[37] The risk of progression is especially related to the aetiology: low (<1%) in viral and idiopathic pericarditis, intermediate (2–5%) in immune-mediated pericarditis and neoplastic pericardial diseases and high (20–30%) in bacterial pericarditis, especially purulent pericarditis.[36] A few large historical series of patients with constrictive pericarditis have been described from tertiary referral centres (Stanford, Mayo Clinic, Cleveland Clinic and Groote Schuur Hospital) reporting cases after pericardiectomy (*Web Table 4*).[90–93] The most common reported causes in developed countries were idiopathic or viral (42–49%), post-cardiac surgery (11–37%), post-radiation therapy (9–31%) (mostly for Hodgkin's disease or breast cancer), connective tissue disorder (3–7%), post-infectious causes (TB or purulent pericarditis in 3–6%) and miscellaneous causes (malignancy, trauma, drug-induced, asbestosis, sarcoidosis, uraemic pericarditis in <10%). TB is now only a rare cause of constrictive pericarditis in developed countries, while it is a major cause in developing countries.[93] However, this disorder may be increasing among immigrants from underdeveloped nations and patients with HIV infection.

3.7.1 Clinical presentation

Constrictive pericarditis is characterized by impaired diastolic filling of the ventricles due to pericardial disease. The classic clinical picture is characterized by signs and symptoms of right heart failure with preserved right and left ventricular function in the absence of previous or concomitant myocardial disease or advanced forms. Patients complain about fatigue, peripheral oedema, breathlessness and abdominal swelling. The delay between the initial pericardial inflammation and the onset of constriction is variable and is possibly a direct evolution from subacute/chronic pericarditis to constrictive pericarditis.[36] Venous congestion, hepatomegaly, pleural effusions and ascites may occur. Haemodynamic impairment of the patient can be additionally aggravated by a systolic dysfunction due to myocardial fibrosis or atrophy in more advanced cases.

Although classic and advanced cases show prominent pericardial thickening and calcifications in chronic forms, constriction may also be present with normal pericardial thickness in up to 20% of the cases.[94] Pericardiectomy is equally successful in those with and without increased pericardial thickness.

3.7.2 Diagnosis

A diagnosis of constrictive pericarditis is based on the association of signs and symptoms of right heart failure and impaired diastolic filling due to pericardial constriction by one or more imaging methods, including echocardiography,[95] CT, CMR, and cardiac catheterization.[2,3,96] The main differential diagnosis is with restrictive cardiomyopathy (*Table 10*).

Recommendations for the diagnosis of constrictive pericarditis

Recommendations	Class[a]	Level[b]	Ref.[c]
Transthoracic echocardiography is recommended in all patients with suspected constrictive pericarditis	I	C	
Chest X-ray (frontal and lateral views) with adequate technical characteristics is recommended in all patients with suspected constrictive pericarditis	I	C	
CT and/or CMR are indicated as second-level imaging techniques to assess calcifications (CT), pericardial thickness, degree and extension of pericardial involvement	I	C	
Cardiac catheterization is indicated when non-invasive diagnostic methods do not provide a definite diagnosis of constriction	I	C	

CMR = cardiac magnetic resonance; CT = computed tomography.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

3.7.3 Therapy

Although the mainstay of treatment of chronic permanent cases is surgery, medical therapy may have a role in at least three conditions. First, medical therapy of specific aetiologies (i.e. tuberculous pericarditis) may be useful to prevent the progression to constriction. Antituberculosis antibiotics may significantly reduce the risk of constriction from >80% to <10%.[79,97]

Second, medical therapy (generally based on anti-inflammatory drugs) may solve the transient constriction occurring in 10–20% of cases within a few months, generally as a temporary phenomenon during the resolution of pericarditis.[51,98,99] The detection of elevated CRP and imaging evidence of pericardial inflammation by contrast enhancement on CT and/or CMR may be helpful to identify patients with potentially reversible forms of constriction where empiric anti-inflammatory therapy should be considered and may prevent the need for pericardiectomy.[100]

Third, medical therapy is supportive and aimed at controlling symptoms of congestion in advanced cases and when surgery is contraindicated or at high risk. In these cases, medical therapy should never delay surgery, if this option is feasible, because advanced cases have a higher mortality and a worse prognosis if surgery is delayed.[51]

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Table 10 Constrictive pericarditis vs. restrictive cardiomyopathy: a brief overview of features for the differential diagnosis (Modified from Imazio *et al.*[51])

Diagnostic evaluation	Constrictive pericarditis	Restrictive cardiomyopathy
Physical findings	Kussmaul sign, pericardial knock	Regurgitant murmur, Kussmaul sign may be present, S3 (advanced).
ECG	Low voltages, non-specific ST/T changes, atrial fibrillation.	Low voltages, pseudoinfarction, possible widening of QRS, left-axis deviation, atrial fibrillation.
Chest X-ray	Pericardial calcifications (1/3 of cases).	No pericardial calcifications.
Echocardiography	• Septal bounce. • Pericardial thickening and calcifications. • Respiratory variation of the mitral peak E velocity of >25% and variation in the pulmonary venous peak D flow velocity of >20% • Colour M-mode flow propagation velocity (Vp) >45 cm/sec. • Tissue Doppler: peak e' >8.0 cm/s.	• Small left ventricle with large atria, possible increased wall thickness. • E/A ratio >2, short DT. • Significant respiratory variations of mitral inflow are absent. • Colour M-mode flow propagation velocity (Vp) <45 cm/sec. • Tissue Doppler: peak e' <8.0 cm/s.
Cardiac Catheterization	'Dip and plateau' or 'square root' sign, right ventricular diastolic, and left ventricular diastolic pressures usually equal, ventricular interdependence (i.e. assessed by the systolic area index >1.1).[a]	Marked right ventricular systolic hypertension (>50 mmHg) and left ventricular diastolic pressure exceeds right ventricular diastolic pressure (LVEDP >RVEDP) at rest or during exercise by 5 mmHg or more (RVEDP <1/3 RVSP).
CT/CMR	Pericardial thickness >3–4 mm, pericardial calcifications (CT), ventricular interdependence (real-time cine CMR).	Normal pericardial thickness (<3.0 mm), myocardial involvement by morphology and functional study (CMR).

CMR = cardiac magnetic resonance; CT = computed tomography; DT= deceleration time; ECG = electrocardiogram; LVEDP = left ventricular end-diastolic pressure; RVEDP= right ventricular end-diastolic pressure; RVSP = right ventricular systolic pressure; S3 = third sound. Kussmaul sign is a paradoxical rise in jugular venous pressure on inspiration.

[a]The systolic area index was defined as the ratio of the RV area (mmHg x s) to the LV area (mmHg x s) in inspiration versus expiration.[96]

Specific diagnostic echocardiographic criteria for the diagnosis of constrictive pericarditis has been recently proposed by the Mayo Clinic and include: septal bounce or ventricular septal shift with either medial e′ >8 cm/s or hepatic vein expiratory diastolic reversal ratio >0.78 (sensitivity 87%, specificity 91%; specificity may increase to 97% if all criteria are present with a correspondent decrease of sensitivity to 64%.[95]

Table 11 Definitions and therapy of main constrictive pericardial syndromes (adapted from Imazio *et al.*[51])

Syndrome	Definition	Therapy
Transient constriction (d.d. permanent constrictive pericarditis, restrictive CMP).	Reversible pattern of constriction following spontaneous recovery or medical therapy.	A 2–3-month course of empiric anti-inflammatory medical therapy.
Effusive-constrictive pericarditis (d.d. cardiac tamponade, constrictive pericarditis).	Failure of the right atrial pressure to fall by 50% or to a level below 10 mmHg after pericardiocentesis. May be diagnosed also by non-invasive imaging.	Pericardiocentesis followed by medical therapy. Surgery for persistent cases.
Chronic constriction (d.d. transient constriction, restrictive CMP).	Persistent constriction after 3–6 months.	Pericardiectomy, medical therapy for advanced cases or high risk of surgery or mixed forms with myocardial involvement.

CMP = cardiomyopathy; d.d. = differential diagnosis.

3.7.4 Specific forms

The classic description of chronic permanent constrictive pericarditis has been challenged by specific forms of constrictive syndromes (i.e. transient constriction, effusive-constrictive forms). Definitions, main differential diagnoses and treatment of the main constrictive pericardial syndromes are summarized in *Table 11*.[51]

3.7.4.1 Transient constrictive pericarditis

A temporary form of constriction usually develops with pericarditis and mild effusion and resolves with anti-inflammatory therapy within several weeks.[98,99] The typical clinical course implies the presence of acute inflammatory pericarditis with constriction due to inflammation, which resolves once the inflammatory process is treated.[98,99] Thus, in the absence of evidence that the condition is chronic (e.g. cachexia, atrial fibrillation, hepatic dysfunction or pericardial calcification), patients with newly diagnosed constrictive pericarditis who are haemodynamically stable may be given a trial of conservative management for 2–3 months before recommending pericardiectomy. Since the inflamed pericardium is enhanced on CT and/or CMR,

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multimodality imaging with CT and CMR may be helpful to detect pericardial inflammation.[2,3,100]

3.7.4.2 *Effusive-constrictive pericarditis*

The pericardial cavity is typically obliterated in patients with constrictive pericarditis. Thus even the normal amount of pericardial fluid is absent. However, pericardial effusion may be present in some cases. In this setting, the scarred pericardium not only constricts the cardiac volume, but can also put pericardial fluid under increased pressure, leading to signs suggestive of cardiac tamponade. This combination is called effusive-constrictive pericarditis.[101]

Effusive-constrictive pericarditis appears to be relatively uncommon in developing countries, with only limited published data.[101] Most cases of effusive-constrictive pericarditis in developed countries are idiopathic, reflecting the frequency of idiopathic pericardial disease in general. However, TB is the most common cause in developing countries.[102] Other reported causes include radiation, neoplasia, chemotherapy, infection (especially TB and purulent forms) and post-surgical pericardial disease.[102]

Patients with effusive-constrictive pericarditis usually have clinical features of pericardial effusion or constrictive pericarditis, or both. The diagnosis of effusive-constrictive pericarditis often becomes apparent during pericardiocentesis in patients initially considered to have uncomplicated cardiac tamponade.[101] For these reasons, it is recommended that intrapericardial pressures, right heart pressures and systemic arterial blood pressure are monitored during elective pericardiocentesis whenever possible. A persistently elevated right atrial pressure after efficient pericardiocentesis may also be due to right heart failure or tricuspid regurgitation.

However, non-invasive imaging may be equally useful for the diagnosis of effusive-constrictive pericarditis.[102] The epicardial layer of pericardium, which is responsible for the constrictive component of this process, is not typically thickened to a degree that is detectable on imaging studies. Nevertheless, careful detection of Doppler findings of constriction can be reported following pericardiocentesis for cardiac tamponade, and effusive-constrictive pericarditis can also be suspected in these cases without haemodynamic monitoring. Useful data may also be provided by CMR. The utility of CMR in constrictive pericardial disease is well established, providing the opportunity not only to evaluate pericardial thickness, cardiac morphology and function, but also for imaging intrathoracic cavity structures, allowing the differentiation of constrictive pericarditis from restrictive cardiomyopathy. Assessment of ventricular coupling with real-time cine magnetic resonance during free breathing allows an accurate evaluation of ventricular interdependence and septal bounce.[2,3]

Since it is the visceral layer of pericardium and not the parietal layer that constricts the heart, visceral pericardiectomy must be performed. However, the visceral component of the pericardiectomy is often difficult, requiring sharp dissection of many small fragments until an improvement in ventricular motion is observed. Thus pericardiectomy for effusive-constrictive pericarditis should be performed only at centres with experience in pericardiectomy for constrictive pericarditis.[101]

3.7.4.3 *Chronic constrictive pericarditis*

Pericardiectomy is the accepted standard of treatment in patients with chronic constrictive pericarditis who have persistent and prominent symptoms such as NYHA class III or IV. However, surgery should be considered cautiously in patients with either mild or very advanced disease and in those with radiation-induced constriction, myocardial dysfunction or significant renal dysfunction. Surgical removal of the pericardium has a significant operative mortality ranging from 6 to 12%.[103–105] Pericardiectomy must be as complete as is technically feasible and should be performed by experienced surgeons. Referral to a centre with a special interest in pericardial disease may be warranted in centres with limited experience in this surgery.

Patients with 'end-stage' constrictive pericarditis derive little or no benefit from pericardiectomy, and the operative risk is inordinately high. Manifestations of end-stage disease include cachexia, atrial fibrillation, a low cardiac output (cardiac index <1.2 l/m^2/min) at rest, hypoalbuminaemia due to protein-losing enteropathy and/or impaired hepatic function due to chronic congestion or cardiogenic cirrhosis.

Prior ionizing radiation is associated with a poor long-term outcome, because it induces cardiomyopathy as well as pericardial disease. Predictors of poor overall survival are prior radiation, worse renal function, higher pulmonary artery systolic pressure, abnormal left ventricular systolic function, lower serum sodium level and older age. Pericardial calcification had no impact on survival.[103–105] Survival after radical pericardiectomy in patients with Child–Pugh (CP) B or C (CP score ≥ 7) was reported to be significantly worse than in patients with CP-A. In multivariable analysis, a CP score ≥ 7, mediastinal irradiation, age and end-stage renal disease (ESRD) identified an increased risk of death after radical pericardiectomy.[106] On this basis, it seems appropriate to apply the CP scoring system for the prediction of mortality after radical pericardiectomy in patients with constrictive pericarditis.

Recommendations for therapy of constrictive pericarditis

Recommendations	Class[a]	Level[b]	Ref.[c]
The mainstay of treatment of chronic permanent constriction is pericardiectomy	I	C	
Medical therapy of specific pericarditis (i.e. tuberculous pericarditis) is recommended to prevent the progression of constriction	I	C	
Empiric anti-inflammatory therapy may be considered in cases with transient or new diagnosis of constriction with concomitant evidence of pericardial inflammation (i.e. CRP elevation or pericardial enhancement on CT/CMR)	IIb	C	

CMR = cardiac magnetic resonance; CRP = C-reactive protein; CT = computed tomography.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

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4. Multimodality cardiovascular imaging and diagnostic work-up

4.1 Multimodality imaging

4.1.1 Chest X-ray

Although chest X-ray can detect pericardial calcifications, presenting as a curvilinear density at the extreme margin of the silhouette, particularly on the lateral view,[107] other techniques (i.e. echocardiography, CT) yield much greater accuracy in assessing the heart and lungs, providing information with regard to cardiac size and the presence of pulmonary pathology (e.g., pulmonary congestion, pneumonia, TB, lung cancer), pleural effusion and hilar and mediastinal enlargement.

4.1.2 Echocardiography

Transthoracic echocardiography is the first-line imaging test in patients with suspected pericardial disease, because it accurately detects pericardial effusion and cardiac tamponade, as well as ventricular dysfunction due to myocardial involvement.[2,3] Although patients with purely fibrinous acute pericarditis may have a normal echocardiogram, the presence of a pericardial effusion is consistent with acute pericarditis and is one of the criteria for its diagnosis.[2,5,6,10,11] Echocardiography may help to differentiate acute pericarditis from myocardial ischaemia by excluding wall motion abnormalities consistent with coronary flow distribution in the setting of patients with acute chest pain. However, ~5% of patients with acute pericarditis and myocardial involvement may demonstrate wall motion abnormalities.

Clinically, two-dimensional echocardiography with Doppler provides the most cost-effective way of diagnosing pericardial effusion and assessing its haemodynamic significance.[48] The size of pericardial effusion on two-dimensional echocardiography is qualitatively assessed by the end-diastolic distance of the echo-free space between the epicardium and parietal pericardium: small (<10 mm), moderate (10–20 mm), large (>20 mm) (*Web Figure 2*).[48]

In order to allow follow-up studies, it is recommended that the images be documented digitally and the effusion size described in a detailed way in the echocardiographic report, including not only the extent, but also the location of each measurement. However, the haemodynamic tolerance is more related to the rapidity of appearance of the effusion than to its total volume.[48,80]

Loculated pericardial effusions or pericardial effusions that contain clots (e.g. after cardiac surgery) may be difficult to diagnose using a transthoracic approach and may require transoesophageal echocardiography.[3,4] Specific findings in pericardial syndromes are discussed in the pertinent paragraphs.

4.1.3 Computed tomography

CT should be regarded as a valuable complementary imaging modality to echocardiography.[3,4,41,108,109] CT is the most accurate technique to image calcified tissue.[2,3] Current multidetector CT scanners combine acquisition speed, high contrast and spatial resolution with volumetric scanning to provide excellent anatomical detail of the heart and pericardium. The anatomical region of interest covered by CT can be limited to the heart and pericardium ('cardiac CT'), although in patients with neoplastic, inflammatory or aortic disease it may encompass the chest entirely and possibly also include the abdomen and pelvis.[108,109] Low-radiation cardiac CT is feasible using prospective electrocardiographic triggering.[108,109] Although the functional consequences of pericardial disease on the heart can be evaluated by CT—at the expense of significantly higher radiation doses—echocardiography and CMR are more appropriate for assessing this feature. Intravenous administration of iodinated contrast material is recommended to increase the density of blood and to depict pericardial inflammation. The normal pericardium is visible as a thin curvilinear structure surrounded by the hypodense mediastinal and epicardial fat, and has a thickness ranging from 0.7 to 2.0 mm. The pericardial sinuses and their respective recesses are visible, in particular when they contain small amounts of pericardial fluid. The main CT findings in pericardial effusion and pericarditis are summarized in *Table 12*.[41,108,109]

In patients with neoplastic disease, pericardial involvement may occur by direct tumour invasion or metastatic spread. CT is important in treatment planning and patient follow-up. The diagnosis of (congenital) pericardial cysts—presenting as well-defined, fluid-dense structures along the left or right heart border—as well as the differential diagnosis with other cystic structures, such as bronchogenic or duplication cysts, is usually straightforward. Finally, CT can be helpful to establish the diagnosis in congenital absence of the pericardium by showing displacement of cardiac structures through the pericardial defect. CT is also essential in the preoperative work-up of some patients with constrictive pericarditis, especially to depict the extension of calcifications and for those with a history of prior cardiothoracic surgery.[109]

4.1.4 Cardiac magnetic resonance

Over the years, CMR has shifted from a morphologic imaging modality towards a comprehensive one, allowing visualization and tissue characterization of the pericardium (and heart) in patients with pericardial disease and appraisal of the consequences of pericardial abnormalities on cardiac function and filling patterns.[110,111] As such, it is probably the preferred imaging modality to optimally assess pericardial disease.[112,113] Cardiac and pericardial morphology are evaluated by dark-blood T1-weighted fast spin-echo and bright-blood cine steady-state free-precession (SSFP) imaging. Cine SSFP imaging has become the reference sequence to assess and quantify cardiac volumes, myocardial mass and ventricular function. When acquired in real-time, this sequence can be used to assess ventricular coupling by assessing the changes in ventricular septal shape and motion over the respiratory cycle.[109,110] Tissue characterization of the heart and pericardium is achieved by dark-blood T1-weighted and dark-blood T2-weighted, short-tau inversion-recovery (STIR) spin-echo imaging, cine SSFP imaging and T1-weighted contrast-enhanced and/or late contrast-enhanced (LCE) imaging following intravenous administration of paramagnetic gadolinium chelates.[3,4,114] The LCE sequence uses an inversion-recovery pre-pulse to increase image contrast and is well suited to visualize pericardial inflammation.[114,115]

Ventricular inflow and venous flow patterns can be evaluated using phase contrast imaging.[111] Similar to CT, the normal

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Table 12 Diagnostic contribution of the different imaging modalities in various pericardial diseases

	Echocardiography	Computerized tomography	Cardiac magnetic resonance
Acute pericarditis	- normal findings in several patients - thickened and hyper-reflective pericardial layers. - variable amount of pericardial fluid - ± intrapericardial fibrinous strands - wall motion abnormalities in myo-pericarditis	- thickened pericardial layers enhancing after contrast administration - abnormalities involving entire pericardium - variable amount of pericardial fluid - ± intrapericardial fibrinous strands.	- thickened pericardial layers - strong pericardial LGE following contrast administration - variable amount of pericardial fluid - ± intrapericardial fibrinous strands - (subepicardial/mid-wall) myocardial LGE in cases of myopericarditis. - inspiratory septal flattening may occur on real-time cine CMR, due to decreased pericardial compliance
Recurrent pericarditis	- similar findings as in acute pericarditis	- similar findings as in acute pericarditis - possibly heterogenous distribution due to fibrotic adhesions - irregular pericardial delineation (fibrotic deformation)	- similar findings as in acute pericarditis - possibly heterogeneous distribution due to fibrotic adhesions. - irregular pericardial delineation (fibrotic deformation)
Constrictive pericarditis	- thickened and hyper-reflective pericardial layers - ± pleural fluid - ± ascites - dilated atria - inspiratory ventricular septal motion toward left ventricle (septal bounce) best documented with M-mode - marked dilation and absent or diminished collapse of the IVC and hepatic veins - premature opening of the pulmonary valve - restrictive filling pattern of RV and LV diastolic filling; - >25 % fall in mitral inflow velocity and >40 % increase in tricuspid velocity in the first beat after inspiration; - opposite changes during expiration; - normal or increased propagation velocity of early diastolic transmitral flow at colour M-mode - decreased expiratory diastolic hepatic vein velocities with large reversals - normal or increased mitral annular velocity (>7 cm/sec) at tissue Doppler - annulus reversus (e' septal >e' lateral)	- thickened pericardial layers ± pericardial calcifications - thickening may be mild to moderate - abnormalities usually most pronounced at the base of the ventricles (RV>LV), atrioventricular grooves and atria - possible extension of fibrocalcific process in adjacent myocardium - compression of cardiac contents by rigid, deformed pericardium - abnormal shape of ventricular septum - dilated atria, caval/hepatic veins hepatic congestion - contrast reversal in caval/hepatic veins - ± pleural fluid - ± ascites - atypical presentations *focal constrictive forms *effusive-constrictive forms	- thickened pericardial layers - pericardial calcifications not visible by CMR! - thickening may be mild to moderate - abnormalities usually most pronounced at the base of the ventricles (RV>LV), atrioventricular grooves and atria - pericardial LGE reflects residual inflammation - possibly extension of fibrocalcific process in adjacent myocardium - compression of cardiac contents by rigid, deformed pericardium - dilated atria, caval/hepatic veins - ± pleural fluid - ± ascites - increased ventricular coupling assessed by real-time cine CMR and/or real-time phase-contrast imaging - fibrotic adhesion of pericardial layers on CMR tagging - atypical presentations *focal constrictive forms *effusive-constrictive forms
Pericardial effusion	- fluid accumulation in pericardial sac and/or pericardial sinuses - pericardial echolucent space throughout cardiac cycle - fluid distribution - semi-quantitative assessment of effusion severity	- fluid accumulation in pericardial sac and/or pericardial sinuses - pericardial width >4 mm regarded as abnormal amount of fluid - advantageous to depict focal effusions and to precisely quantitate the amount of fluid - attenuation values of pericardial fluid (HU) yield information with regard to nature of fluid *simple effusion: 0–20 HU *proteinaceous/haemorrhagic: >20 HU *if very high HU, suspect intrapericardial leakage of contrast (e.g. ruptured aortic dissection) *chylopericardium: negative HU values *pneumopericardium: air (use specific window/center settings) - pericardial layers have normal thickness, *if thickened and enhancing: suspect inflammation *if thickened and calcified, rule out constrictive pericarditis - may be associated with pericardial tamponade - CT of the heart may be part of a more extended examination including the remainder of the chest ± abdomen	- fluid accumulation in pericardial sac and/or pericardial sinuses - pericardial width >4 mm regarded as abnormal amount of fluid - advantageous to depict focal effusions and to precisely quantitate the amount of fluid - combination of sequences with different 'weighting' yield information with regard to the nature of the effusion - pericardial layers have normal thickness, *if thickened and enhancing suspect inflammation - advantageous to evaluate the remainder of the heart: *myocardial tissue characterisation (oedema, infarction, inflammation, fibrosis) *myocardial/valvular function *inflow patterns - may be associated with pericardial tamponade
Cardiac tamponade	- semi-quantitative assessment of effusion severity - fluid distribution - assessment of its haemodynamic impact - guide and monitoring pericardiocentesis - re-evaluation for timing catheter removal		

CMR = cardiac magnetic resonance; CT = computed tomography; HU = Hounsfield units; IVC = inferior vena cava; LGE= late gadolinium enhancement; LV = left ventricle; RV = right ventricle.

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pericardium appears on T1-weighted imaging as a thin hypointense ('dark') curvilinear structure surrounded by hyperintense ('bright') mediastinal and epicardial fat. Normal pericardial thickness ranges from 1.2 to 1.7 mm. The imaging characteristics of pericardial effusion and pericarditis at CMR are shown in *Table 12*. It should be emphasized that CMR can accurately distinguish between mixed myopericardial diseases such as mixed inflammatory forms (e.g. myopericarditis or perimyocarditis) and post-myocardial infarction pericardial injury.[116,117] In patients with constrictive pericarditis, CMR is particularly important in the diagnosis of atypical presentations, such as those with minimally thickened pericardium or effusive-constrictive pericarditis, and those with potentially reversible or transient forms of constrictive pericarditis, showing enhancement of the pericardial layers at LCE imaging.[115,118,119] Compared with CT, CMR has the advantage of providing information with regard to the haemodynamic consequences of the non-compliant pericardium on cardiac filling,[109–111] and has the potential of showing fibrotic fusion of pericardial layers.[120]

In patients with congenital pericardial pathology and pericardial malignancy, CMR shares the advantages of CT, but allows better tissue characterization and the possibility of evaluating the functional consequences.[121] Moreover, novel techniques, such as diffusion-weighted and dynamic contrast-enhanced magnetic resonance imaging, open perspectives for improved tissue characterization in patients with pericardial tumours.[122]

4.1.5 Nuclear medicine

In selected cases, positron emission tomography (PET) alone, or preferably in combination with CT (PET/CT), can be indicated to depict the metabolic activity of pericardial disease. Pericardial uptake of ^{18}F-fluorodeoxyglucose (FDG) tracer in patients with solid cancers and lymphoma is indicative of (malignant) pericardial involvement, thus providing essential information on the diagnosis, staging and assessment of the therapeutic response.[123] The uptake is usually intense and often associated with a focal soft tissue mass.[124] PET/CT is also of value in identifying the nature of inflammatory pericarditis. In particular, tuberculous pericarditis yields higher FDG uptakes than idiopathic forms.[125] However, differentiation between benign and malignant pericardial disease, as well as differentiation between physiological and pathological cardiac FDG uptake by PET/CT, remains challenging.[123]

4.1.6 Cardiac catheterization

Cardiac catheterization is not routinely used for the diagnosis of pericardial disease, as current non-invasive techniques are usually able to solve the differential diagnosis of a patient with the suspicion of heart disease involving the pericardium. However, right heart catheterization may be useful in certain circumstances. Early recognition of abnormal haemodynamics related to cardiac tamponade during invasive procedures (i.e. epicardial ablation, percutaneous aortic valve implantation, complex angioplasty or complex procedures involving trans-septal punctures, among others) may help avoid serious consequences for the patient. In addition, the differentiation between constrictive pericarditis and restrictive cardiomyopathy is sometimes difficult and may require an invasive test.

In cardiac tamponade, the right atrial pressure waveform has an attenuated or an absent Y-descent. Absent Y-descent is secondary to diastolic equalization of pressures in the right atrium and right ventricle and lack of effective flow across the tricuspid valve in early ventricular diastole. Also, equalization of mean right atrial, right ventricular and pulmonary artery diastolic pressures and mean pulmonary capillary wedge pressures can be present. Other haemodynamic abnormalities include elevation of filling pressures in all four cardiac chambers, right ventricle and left ventricle peak systolic pressures out of phase, peak aortic pressure varying more than 10–12 mmHg and a decrease in cardiac output.[126,127]

The differentiation of constrictive pericarditis from restrictive cardiomyopathy remains difficult. Visualization of the pericardium by CT or CMR may help in detecting an abnormal pericardium. But these tests provide anatomical information and do not necessarily reflect the pathophysiological abnormality present. Also, patients with surgically proven constrictive pericarditis may have a normal-appearing pericardium on imaging studies. Alternatively patients may have abnormal pericardial thickness in the absence of constriction, especially after radiation therapy or prior cardiac surgery. Classically, direct measurements of pressures show M- or W-shaped atrial pressure waveforms and 'square root' or 'dip-and-plateau' right ventricular pressure waveforms, reflecting impaired ventricular filling. End-diastolic pressure equalization (typically within 5 mmHg) occurs between these cardiac chambers in constrictive pericarditis because of the fixed and limited space within the thickened and stiff pericardium. Pulmonary artery systolic pressures are usually normal in pericardial constriction; higher pulmonary pressures suggest a restrictive cardiomyopathy.[126]

Recently a novel haemodynamic parameter has been tested to differentiate both entities.[96] Specifically, the ratio of the right ventricular to left ventricular systolic pressure–time area during inspiration versus expiration (systolic area index) was used as a measurement of enhanced ventricular interaction. In patients with surgically documented constrictive pericarditis, during inspiration there is an increase in the area of the right ventricular pressure curve compared with expiration. The area of the left ventricular pressure curve decreases during inspiration as compared with expiration. In contrast, patients with restrictive myocardial disease documented by endomyocardial biopsy usually present a decrease in the area of the right ventricular pressure curve during inspiration as compared with expiration. The area of the left ventricular pressure curve is unchanged during inspiration as compared with expiration. This systolic area index presented a 97% sensitivity and 100% predictive accuracy for identifying patients with surgically proven constrictive pericarditis.[96]

4.1.7 Multimodality imaging

Echocardiography, cardiac CT and CMR are often used as complementary imaging modalities (*Table 13*). The choice of one or multiple imaging modalities is driven by the clinical context or condition of the patient. A modern approach for the management of pericardial diseases should include the integration of different imaging modalities in order to improve the diagnostic accuracy and clinical management of patients.[2,3]

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Table 13 Comparison of non-invasive imaging modalities to study the pericardium

	TTE	CT	CMR
Technical aspects			
Availability	+++	++	+
Cost	Low	Moderate	High
Exam duration (minutes)	15–30	10	30–40
Safety	+++	+[a]	++[b]
Pt access and monitoring	+++	++	+/-
Pericardium			
Pericardial thickness	+/-	+++	+++
Pericardial calcifications	+	+++	-
Pericardial inflammation	+/-	++	+++
Motion layers (adhesions)	++	+	+++
Effusion detection	++	+++	+++
Effusion characterization	+	++	++
Pericardial masses	+	+/++	++/+++
Guiding/monitoring pericardiocentesis	+++	-	-
Cardiac morphology			
(Including tissue characterization)	++	++	+++
Cardiac function			
Systolic	+++	++[c]	+++
Diastolic function	+++	-	++
Septal motion (coupling)	+++	+/-	+++
Respiratory changes	++	+/-	++

CMR = cardiac magnetic resonance magnetic resonance; CT = computed tomography; ECG = electrocardiogram; TTE = transthoracic echocardiography.
(-) not possible or poor; (+) moderate; (++) good; (+++) excellent.
[a]Ionizing radiation, potential nephrotoxicity of contrast medium, allergic reactions to contrast.
[b]Patients with metallic implants, claustrophobia, potential nephrotoxicity of contrast medium, allergic reactions to contrast, restricted only to haemodynamically stable patients.
[c]Use of ECG synchronized data acquisition.

4.2 Proposal for a general diagnostic work-up

In the management of pericardial syndromes, a major controversy is the role of an extensive aetiological search and admission for all patients with pericarditis or pericardial effusion.[1,4,6,51] The epidemiological background is essential to develop a rational cost-effective management programme and the clinician should especially identify causes that require targeted therapies.[4,5,51,128–130] The approach may be different for research, when we attempt to reduce the number of 'idiopathic' cases. The diagnosis of idiopathic cases is essentially an exclusion diagnosis, supported by a typical clinical course.

On this basis, auscultation, ECG, echocardiography, chest X-ray, routine blood tests, including markers of inflammation (i.e., CRP and/or ESR) and myocardial lesions (CK, troponins), are recommended in all cases of suspected pericarditis. Additional testing should be related to the suspected origin and clinical presentation.[5,6,128–130]

The major specific causes to be ruled out are bacterial pericarditis (especially TB), neoplastic pericarditis and pericarditis associated with a systemic disease (generally an autoimmune disease) (*Web Table 5*).[9,77,129–131] Each of these specific causes has a frequency of ~5% of all unselected cases of pericarditis from developed countries (*Web Table 5*),[9,77,129–131] while frequencies increase in moderate to large pericardial effusions (*Web Table 3*).[8,74–78] Emerging additional causes include iatrogenic ones (percutaneous coronary interventions, pacemaker insertion, catheter ablation).[132] The aetiological spectrum is different in developing countries with a high prevalence of TB (e.g. 70–80% of pericarditis in sub-Saharan Africa, and often associated with HIV infection).[52,79]

Certain clinical features at presentation may be associated with an increased risk of specific aetiologies (non-viral or non-idiopathic) and complications during follow-up (recurrences, tamponade, constriction) and are suggested as 'high-risk features' useful for the triage of pericarditis to establish the need for a full aetiological search and admission in a single patient (*Figure 1*, *Web Table 6*).[8,9] Factors indicated as 'major' have been validated by multivariate analysis, while factors indicated as 'minor' are based on expert opinion and literature review:[9] they are essentially theoretical risk factors for complications and suggest the indication for admission and close monitoring of the evolution. Major risk factors include fever >38°C [hazard ratio (HR) 3.56], subacute course (symptoms developing over several days or weeks; HR 3.97), large pericardial effusion (diastolic echo-free space >20 mm in width) or cardiac tamponade (HR 2.15) and failure of aspirin or NSAIDs (HR 2.50).[9] Large effusion and tamponade (HR 2.51) and aspirin or NSAIDs failure (HR 5.50) also identify an increased risk of complications during follow-up (recurrences, tamponade, constriction).[9] Minor risk factors are pericarditis associated with myocarditis, immunodepression, trauma and oral anticoagulant therapy.

For patients with predictors of poor prognosis, major or minor (*Figure 1*), hospitalization and a full aetiological search are warranted.[5,6,8,9,128] In contrast, when these negative predictors are absent, patients are at low risk of specific causes and complications, and outpatient management may be considered.[8] This approach is safe without an excess of complications and new unexpected diagnoses requiring a specific therapy.[8,9,128] The

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Table 14 First and second level investigations for pericarditis

Level	Investigation
1st level (all cases)	Markers of inflammation (i.e. ESR, CRP, white blood cell count). Renal function and liver tests, thyroid function. Markers of myocardial lesion (i.e. troponins, CK). ECG Echocardiography Chest X-ray
2nd level (if 1st level not sufficient for diagnostic purposes)	CT and/or CMR Analysis of pericardial fluid from pericardiocentesis, or surgical drainage, for (i) cardiac tamponade or (ii) suspected bacterial, neoplastic pericarditis, or (iii) symptomatic moderate to large effusions not responding to conventional anti-inflammatory therapy. Additional testing should be directed to specific aetiologies according to clinical presentation (presence of high risk clinical criteria).

CK = creatine kinase; CMR = cardiac magnetic resonance; CRP = C-reactive protein; CT = computed tomography; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate.

Table 15 Main analyses to be performed on pericardial fluid

Analysis	Test
General chemistry	Protein level >3 g/dL, protein fluid/serum ratio >0.5, LDH >200 IU/L, fluid/serum ratio >0.6[a], blood cell count.
Cytology	Cytology (higher volumes of fluid, centrifugation, and rapid analysis improve diagnostic yield).
Polymerase chain reaction (PCR)	PCR for TB.
Microbiology	Mycobacterium cultures, aerobic and anaerobic cultures.

LDH = lactate dehydrogenase; TB = tuberculosis.
[a]High values of protein and LDH are commonly interpreted as an exudate, as in pleural fluid, but have not been validated for pericardial fluid.

same approach is also useful for patients with recurrences who may generally be treated as outpatients, unless predictors of poor prognosis are present or a specific cause can be ruled out. With a clear diagnosis of idiopathic origin and a recurrence course with complete symptom-free periods between the episodes, it is also unnecessary to repeat a new aetiological search at each recurrence unless new clinical features become evident. First- and second-line general investigations are reported in the recommendations and *Tables 14–16*.

Recommendations for the general diagnostic work-up of pericardial diseases

Recommendations	Class[a]	Level[b]	Ref.[c]
In all cases of suspected pericardial disease a first diagnostic evaluation is recommended with – auscultation – ECG – transthoracic echocardiography – chest X-ray – routine blood tests, including markers of inflammation (i.e., CRP and/or ESR), white blood cell count with differential count, renal function and liver tests and myocardial lesion tests (CK, troponins)	I	C	
It is recommended to search for independent predictors of an identifiable and specifically treatable cause of pericarditis (i.e. bacterial, neoplastic, systemic inflammatory diseases). Major factors include – fever >38°C – subacute course (symptoms developing over several days or weeks) – large pericardial effusion (diastolic echo-free space >20 mm in width) – cardiac tamponade – failure of aspirin or NSAIDs	I	B	8,9
CT and/or CMR are recommended as second-level testing for diagnostic workup in pericarditis	I	C	
Pericardiocentesis or surgical drainage are indicated for cardiac tamponade or suspected bacterial and neoplastic pericarditis	I	C	
Percutaneous or surgical pericardial biopsy may be considered in selected cases of suspected neoplastic or tuberculous pericarditis	IIb	C	
Further testing is indicated in high-risk patients (defined as above) according to the clinical conditions	I	C	

CK = creatine kinase; CMR = cardiac magnetic resonance; CRP = C-reactive protein; CT = computed tomography; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; NSAIDs = non-steroidal anti-inflammatory drugs.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

5. Specific aetiologies of pericardial syndromes

5.1 Viral pericarditis

5.1.2 Definition and clinical spectrum

Most cases of acute pericarditis in developed countries are based on viral infections or are autoreactive.[5,6,133–135] Acute viral pericarditis

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Table 16 Suggested diagnostic flowchart in some common conditions in high risk patients

Clinical condition	Blood tests	Imaging	Pericardial fluid[a]	Others
Probable autoimmune condition	- ANA, ENA, ANCA (ACE and 24 h urinary calcium - if sarcoidosis is suspected) - Ferritin if Still disease is suspected.	Consider PET if large vessel arteritis (Horton or Takayasu) or Sarcoidosis is suspected.		Specialist consultation may be useful. Hypereosinophilia (Churg Strauss), oral and genital apthae (Behcet); difference in blood pressure between two arms (Takayasu), dry eyes (Sjögren, Sarcoidosis) macroglossia (amyloidosis).
Probable TB	IGRA test (i.e Quantiferon, ELISpot, etc).	Chest CT Scan	- Acid-fast bacilli staining, mycobacterium cultures, - PCR for genome. Adenosine deaminase >40 U/l, unstimulated IFN-gamma.	- Culture and PCR in sputum and other biological fluids - Consider pericardial biopsy.
Probable neoplasm	Specific neoplastic markers not specific or sensitive (CA 125 is often non-specifically elevated in the blood when serosal effusions are present).	Chest and abdomen CT scan, consider PET.	Cytology (higher volumes of fluid, centrifugation, and rapid analysis improve diagnostic yield). Tumour markers (e.g. CEA >5 ng/ml or CYFRA 21–1 >100 ng/ml).	Consider pericardial biopsy.
Probable viral infections	- Genome search with PCR is now preferred to serology for most viruses[b]. - Consider serology for HCV and HIV		Genome search with PCR for specific infectious agents, e.g. enteroviruses, adenoviruses, parvovirus B19, HHV-6, CMV, EBV[b].	Infectious specialist consultation in case of positivity.
Probable bacterial infections	- Blood cultures before antibiotics. - Serology for *Coxiella burnetii* if Q-fever is suspected. - Serology for *Borrelia spp.* if Lyme disease is suspected.	Chest CT scan	- Aerobic and anaerobic cultures. - Glucose	Consider pericardial biopsy.
Probable autoinflammatory conditions (periodic fevers)	FMF and TRAPS mutations.			Possible clues for TRAPS are familial forms and poor response to colchicine.
Chronic pericardial effusion	TSH. Renal function tests.			Consider appropriate tests for suspected neoplasms and TB.
Probable constriction	BNP (near-normal).	Cardiac MR, chest CT scan, biventricular catheterization.		All the tests for suspected TB.

ACE = angiotensin-converting enzyme; ANA = anti-nuclear antibodies; ANCA = anti-neutrophil cytoplasm antibodies; BNP = brain natriuretic peptide; CEA = carcinoembryonic antigen; CMV = cytomegalovirus; CT = computed tomography; EBV = Epstein-Barr virus; ENA = anti-extractable nuclear antigens; FMF = familial Mediterranean fever; HCV = hepatitis C virus; HHV = human herpesvirus; HIV = human immunodeficiency virus; IGRA = interferon-gamma release assay; MR = magnetic resonance; PCR = polymerase chain reaction; PET = positron emission tomography; spp = species; TB = tuberculosis; TRAPS = tumour necrosis factor receptor-associated periodic syndrome; TSH = thyroid stimulating hormone.
[a]Consider storage of a sterile sample for further analyses.
[b]See viral pericarditis section—at present, these investigations have no therapeutic or prognostic implications.
IGRAs are whole-blood tests that can aid in diagnosing Mycobacterium tuberculosis infection. They do not help to differentiate latent TB infection from TB disease.

often presents as a self-limited disease, with most patients recovering without complications.[5,6,9,36] However, as a consequence of acute viral pericarditis, cardiac tamponade, recurrent pericarditis and, more rarely, constrictive pericarditis may also develop.[36]

5.1.3 Pathogenesis

Cardiotropic viruses can cause pericardial and myocardial inflammation via direct cytolytic or cytotoxic effects (e.g. enteroviruses) and/or via T and/or B cell–driven immune-mediated mechanisms (e.g. herpesviruses). Persistence of viral nucleic acid without virus replication in the peri(myo)cardium is known to sustain ongoing inflammation and effusions via (auto)immune processes directed against specific cardiac proteins by molecular mimicry.[133]

5.1.4 Diagnosis

The definite diagnosis of viral pericarditis requires a comprehensive workup of histological, cytological, immunohistological and molecular investigations in pericardial fluid and peri-/epicardial biopsies

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obtained in conjunction with pericardioscopy, permitting the evaluation of possible algorithms for a causative therapy.[133] In contrast, serological tests were found to be futile in the diagnosis of viral pericarditis. Whereas no up-regulation of pro-inflammatory cytokine expression is noted in the serum, TNF-α, vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), IL-6, IL-8 and interferon-gamma (IFN-γ) are increased in the pericardial effusions of patients with pericarditis, indicating the presence of local inflammatory reactions.[134,135] Accordingly, there is no correlation of antiviral antibodies in the serum or virus isolation from throat or rectal swabs with positive molecular polymerase chain reaction (PCR)/*in situ* hybridization analyses for the detection of cardiotropic viruses in pericardial tissue and fluid.[136]

5.1.5 Identification of viral nucleic acids

Mainly by quantitative PCR techniques, nucleic acids of different cardiotropic RNA and DNA viruses have been detected in epicardial and pericardial biopsies and the pericardial fluid of children and adults with acute pericarditis, but also in patients with recurring and constrictive pericarditis.[133,137] Regarding RNA viruses, various subtypes of enteroviruses including echoviruses and coxsackieviruses of groups A (A4, A16) and B (CVB2, CVB3, CVB4) were identified in patients with acute and constrictive pericarditis.[137,138] Among the RNA viruses, influenza A viruses (e.g. H1N1, H5N1, H3N2) and occasionally chikungunya virus, human coronavirus NL-63, respiratory syncytial virus and dengue virus infections were suspected as aetiopathogenic agents in pericarditis.

Compared with RNA viruses, nucleic acids of DNA viruses, including parvovirus B19 and herpesviruses [Epstein–Barr virus (EBV) and human herpesvirus 6 (HHV-6)], are present in pericardial biopsies and pericardial fluid at greater frequencies and higher viral DNA copy numbers.[133] Whereas parvovirus B19, with up to 7×10^6 GE/lg DNA was predominantly detected in epicardial tissue, EBV was most frequently found in pericardial fluid.[133] DNA of varicella zoster virus, herpes simplex virus and adenoviruses is only rarely detected in pericarditis patients. Cytomegalovirus (CMV)-associated pericarditis is mainly found in immunocompromised and HIV patients.[1] In developing countries with a delayed roll-out of antiretroviral therapy, HIV-associated inflammatory reactions (often related to TB) of the pericardium and myocardium are common complications.[139] However, at present these investigations are usually not performed because of their complexity, cost, invasive nature and low availability.

5.1.6 Therapy

Acute viral pericarditis often presents as a self-limiting disease that responds well to a short course of treatment with NSAIDs, with the adjunct of colchicine, especially for prevention of recurrences.[4–6,50,58,59] The identification of specific viral signatures aids in understanding the pathogenetic mechanisms in pericarditis, and might enable an individualized aetiologically driven specific treatment approach to be established by distinguishing a viral aetiology from autoreactive inflammation.[133] Some experts suggest antiviral treatment similar to that for myocarditis (IVIG therapy in acute systemic enteroviral, CMV, EBV and parvovirus B19 infection, oral valganciclovir in HHV-6 perimyocarditis, IFN-α for enteroviral pericarditis).[133] However, these treatments are still under evaluation and rarely used. Involvement of infectious disease specialists is recommended. So far, no therapy is available to solve the problem of virus persistence and consecutive inflammation, particularly when induced by herpesviruses and parvovirus B19 infections.[133] Importantly, corticosteroids are generally not indicated in viral pericarditis, as they are known to reactivate many virus infections and thus lead to ongoing inflammation.[133]

Recommendations for the diagnosis and therapy of viral pericarditis

Recommendations	Class[a]	Level[b]	Ref.[c]
For the definite[d] diagnosis of viral pericarditis, a comprehensive workup of histological, cytological, immunohistological and molecular investigations in pericardial fluid and peri-/epicardial biopsies should be considered	IIa	C	
Routine viral serology is not recommended, with the possible exception of HIV and HCV	III	C	
Corticosteroid therapy is not recommended in viral pericarditis	III	C	

HCV = hepatitis C virus; HIV = human immunodeficiency virus.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]In the absence of such an argument, the term 'presumed viral pericarditis' should be used.

5.2 Bacterial pericarditis

Bacterial pericarditis is relatively uncommon in clinical practice in developed countries with a low prevalence of TB. Tuberculous pericarditis is the most common form all over the world and the most common cause of pericardial diseases in developing countries. We will discuss this form and also purulent pericarditis, which is less common.

5.2.1 Tuberculous pericarditis

Tuberculous pericarditis accounts for ≤4% of pericardial disease in the developed world.[5,6,52]. In contrast, TB is the cause of clinically significant pericardial effusion in >90% of HIV-infected and 50–70% of non-HIV-infected individuals who live in developing countries where TB is endemic.[77] The disease can occur at any age, and men are affected more frequently than women.[140] Clinical evidence of chronic cardiac compression mimicking congestive heart failure is the most common presentation.[79,93] Clinical presentations are pericardial effusion, effusive-constrictive pericarditis and constrictive pericarditis.[79] Tuberculous pericarditis has a mortality rate of 17–40% at 6 months after diagnosis.[141] It should be emphasized that the majority of the information on tuberculous

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pericarditis comes from endemic areas in underdeveloped countries and immunodepressed patients. The applicability of this information to the Western world is questionable.

5.2.1.1 Diagnosis

A 'definite' diagnosis of tuberculous pericarditis is based on the presence of tubercle bacilli in the pericardial fluid or on histological section of the pericardium, by culture or by PCR (Xpert MTB/RIF) testing; a 'probable' diagnosis is made when there is proof of TB elsewhere in a patient with unexplained pericarditis, a lymphocytic pericardial exudate with elevated unstimulated interferon-gamma (uIFN-γ), adenosine deaminase (ADA) or lysozyme levels and/or an appropriate response to antituberculosis chemotherapy in endemic areas.[79] uIFN-γ offers superior accuracy for the diagnosis of microbiologically confirmed tuberculous pericarditis compared with the ADA assay and the Xpert MTB/RIF test.[142] A protocol for the evaluation of suspected tuberculous pericardial effusion is proposed in *Table 17*.

5.2.1.2 Management

A regimen consisting of rifampicin, isoniazid, pyrazinamide and ethambutol for at least 2 months followed by isoniazid and rifampicin (total of 6 months of therapy) is effective in treating extrapulmonary TB. Treatment for ≥9 months gives no better results and has the disadvantages of increased cost and increased risk of poor compliance.[143]

The evolution towards constrictive pericarditis is a serious potential complication. Constriction generally develops within 6 months of presentation with effusive pericarditis (effusive-constrictive pericarditis).[79] Tuberculous pericardial constriction is almost always associated with pericardial thickening. Prior to the introduction of effective TB chemotherapy, up to 50% of patients with effusive tuberculous pericarditis progressed to constriction. Rifampicin-based antituberculosis treatment reduced the incidence of constriction to 17–40%. Appropriate antibiotic therapy is essential to prevent this progression.[79,144] In addition, two interventions may reduce the incidence of constriction: the first is intrapericardial urokinase[145] and second, the Investigation of the Management of Pericarditis (IMPI) trial has shown that high-dose adjunctive prednisolone reduces the incidence of constrictive pericarditis by 46% regardless of HIV status.[97]

Adjunctive corticosteroid therapy with prednisolone for 6 weeks had a neutral effect on the combined outcome of death from all causes, cardiac tamponade requiring pericardiocentesis or pericardial constriction; however, this therapy was associated with an increased risk of HIV-associated malignancies in the prednisolone-

Table 17 A step-wise protocol for the evaluation of suspected tuberculous pericarditis and pericardial effusion

Stage 1: Initial non-invasive evaluation	• Chest radiograph may reveal changes suggestive of pulmonary tuberculosis in 30% of cases. • Echocardiogram: the presence of a large pericardial effusion with frond-like projections, and thick 'porridge-like' fluid is suggestive of an exudate but not specific for a tuberculous aetiology. • CT scan and/or MRI of the chest are alternative imaging modalities where available: look for evidence of pericardial effusion and thickening (>3 mm), and typical mediastinal and tracheobronchial lymphadenopathy (>10 mm, hypodense centres, matting), with sparing of hilar lymph nodes. • Culture of sputum, gastric aspirate, and/or urine for *Mycobacterium tuberculosis (M. tuberculosis)* should be considered in all patients. • Scalene lymph node biopsy if pericardial fluid is not accessible and lymphadenopathy present. • Tuberculin skin test is not helpful in adults regardless of the background prevalence of tuberculosis. • If pericardial fluid is not accessible, a diagnostic score of ≥6 based on the following criteria is highly suggestive of tuberculous pericarditis in people living in endemic areas: fever (1), night sweats (1), weight loss (2), globulin level >40 g/L (3) and peripheral leucocyte count <$10x10^9$ /L (3).
Stage 2: Pericardiocentesis	• *Therapeutic pericardiocentesis* is absolutely indicated in the presence of cardiac tamponade. • *Diagnostic pericardiocentesis* should be considered in all patients with suspected tuberculous pericarditis, and the following tests performed on the pericardial fluid: 1. Direct inoculation of the pericardial fluid into double strength liquid Kirchner culture medium (or equivalent medium), and culture for *M. tuberculosis*. 2. Quantitative polymerase chain reaction (Xpert MTB/RIF) testing for nucleic acids of *M. tuberculosis*. 3. Biochemical tests to distinguish between an exudate and a transudate (fluid and serum protein; fluid and serum LDH). 4. White cell analysis and count, and cytology: a lymphocytic exudate favours tuberculous pericarditis. 5. Indirect tests for tuberculous infection: interferon-gamma (IFN-γ), adenosine deaminase (ADA), or lysozyme assay.
Stage 3: Pericardial biopsy	• *"Therapeutic" biopsy:* as part of surgical drainage in patients with cardiac tamponade relapsing after pericardiocentesis or requiring open drainage of pericardial fluid for reasons such as repeated accumulation of pericardial fluid or failure to respond to empiric medical therapy. • *Diagnostic biopsy:* In areas where tuberculosis is endemic, a diagnostic biopsy is not required prior to commencing empiric antituberculosis treatment. In areas where tuberculosis is not endemic, a diagnostic biopsy is recommended in patients with >3 weeks of illness and without aetiologic diagnosis having been reached by other tests.
Stage 4: Empiric antituberculosis chemotherapy	• *Tuberculosis endemic in the population:* trial of empiric antituberculosis chemotherapy is recommended for exudative pericardial effusion, after excluding other causes such as malignancy, uraemia, trauma, purulent pericarditis, and auto-immune diseases. • *Tuberculosis not endemic in the population:* when systematic investigation fails to yield a diagnosis of tuberculous pericarditis, there is no justification for starting antituberculosis treatment empirically.

ADA = adenosine deaminase; CT = computed tomography; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; TB = tuberculosis.

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treated group.[97] Adjunctive steroid therapy was associated with a reduced incidence of pericardial constriction and hospitalization. The beneficial effects of prednisolone on constriction and hospitalization were similar in HIV-positive and HIV-negative patients. On this basis, it may be reasonable to use adjunctive corticosteroids in patients with tuberculous pericarditis without HIV infection and to avoid them in HIV-infected individuals because of the increased risk of malignancy.[97]

Recommendations for the diagnosis and treatment of tuberculous pericarditis and effusion

Recommendations	Class[a]	Level[b]	Ref.[c]
Diagnostic pericardiocentesis should be considered in all patients with suspected tuberculous pericarditis	IIa	C	
Intrapericardial urokinase may be considered to reduce the risk of constriction in tuberculous effusive pericarditis	IIb	C	
In patients living in non-endemic areas, empiric antituberculosis treatment is not recommended when systematic investigation fails to yield a diagnosis of tuberculous pericarditis	III	C	
In patients living in endemic areas, empiric antituberculosis chemotherapy is recommended for exudative pericardial effusion, after excluding other causes	I	C	
Adjunctive steroids may be considered in HIV-negative cases of TB pericarditis and avoided in HIV-associated TB pericarditis	IIb	C	

HIV = human immunodeficiency virus; TB = tuberculosis.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Recommendations for the general management of constrictive tuberculous pericarditis

Recommendations	Class[a]	Level[b]	Ref.[c]
Standard antituberculosis drugs for 6 months is recommended for the prevention of tuberculous pericardial constriction	I	C	
Pericardiectomy is recommended if the patient's condition is not improving or is deteriorating after 4–8 weeks of antituberculosis therapy	I	C	

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

5.2.2 Purulent pericarditis

5.2.2.1 Epidemiology

Purulent pericarditis is rare, accounting for <1% of cases.[5,6] In Western series, the most common organisms have been staphylococci, streptococci and pneumococci, while the predominant associated lesions were empyema (50%) or pneumonia (33%).[146] In immunosuppressed patients or following thoracic surgery, *Staphylococcus aureus* (30%) and fungi (20%) are more common.[147] Also, anaerobes originating from the oropharynx have been reported.[148] Seeding may be haematogenous or by contiguous spread from the retropharyngeal space, cardiac valves and below the diaphragm.[149] *Neisseria meningitidis* may involve the pericardium either through initiating an immune-mediated sterile effusion or by direct infection and purulent reaction. The modern era of iatrogenic and HIV-associated immunosuppression has witnessed more unusual organisms.

5.2.2.2 Diagnosis

Purulent pericarditis is rare and generally manifested as a serious febrile disease. The underlying sepsis may predominate the illness.[146–149] Suspicion of purulent pericarditis is an indication for urgent pericardiocentesis,[1,5,12] which is diagnostic. The fluid may be frankly purulent. A low pericardial:serum glucose ratio (mean 0.3) and elevated pericardial fluid white cell count with a high proportion of neutrophils (mean cell count 2.8/μl, 92% neutrophils) differentiate purulent from tuberculous (glucose ratio 0.7, count 1.7/μl, 50% neutrophils) and neoplastic (glucose ratio 0.8, count 3.3/μl, 55% neutrophils) pericarditis.[150] Fluid should be sent for bacterial, fungal and tuberculous studies, with blood for cultures and other samples being taken as guided by the clinical presentation.[12]

5.2.2.3 Management

Purulent pericarditis should be managed aggressively, as death is inevitable if untreated, whereas with comprehensive therapy 85% of cases have been reported to survive the episode and have a good long-term outcome.[50,146] Intravenous antimicrobial therapy should be started empirically until microbiological results are available. Drainage is crucial. Purulent effusions are often heavily loculated and likely to rapidly re-accumulate. Intrapericardial thrombolysis is a possible treatment for cases with loculated effusions in order to achieve adequate drainage before resorting to surgery.[151] Subxiphoid pericardiostomy and rinsing of the pericardial cavity should be considered.[1] This allows more complete drainage of the effusion, as loculations can be manually lysed.

Recommendations for the diagnosis of purulent pericarditis

Recommendations	Class[a]	Level[b]	Ref.[c]
Urgent pericardiocentesis is recommended for the diagnosis of purulent pericarditis	I	C	
It is recommended that pericardial fluid be sent for bacterial, fungal and tuberculous studies and blood drawn for cultures	I	C	

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

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Recommendations for the therapy of purulent pericarditis

Recommendations	Class[a]	Level[b]	Ref.[c]
Effective pericardial drainage is recommended for purulent pericarditis	I	C	
Administration of intravenous antibiotics is indicated to treat purulent pericarditis	I	C	
Subxiphoid pericardiotomy and rinsing of the pericardial cavity should be considered	IIa	C	
Intrapericardial thrombolysis should be considered	IIa	C	
Pericardiectomy for dense adhesions, loculated or thick purulent effusion, recurrence of tamponade, persistent infection and progression to constriction should be considered	IIa	C	

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Recommendations for the management of pericarditis in renal failure

Recommendations	Class[a]	Level[b]	Ref.[c]
Dialysis should be considered in uraemic pericarditis	IIa	C	
When patients with adequate dialysis develop pericarditis, intensifying dialysis should be considered	IIa	C	
Pericardial aspiration and/or drainage may be considered in non-responsive patients with dialysis	IIb	C	
NSAIDs and corticosteroids (systemic or intrapericardial) may be considered when intensive dialysis is ineffective	IIb	C	
Colchicine is contraindicated in patients with pericarditis and severe renal impairment (see *Web Table 1B*)	III	C	

NSAIDs = non-steroidal anti-inflammatory drugs.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

5.3 Pericarditis in renal failure

Renal disease and overall ESRD are associated with possible pericardial involvement.[152] Three different pathologies are found in uraemic patients: uraemic pericarditis—before renal replacement therapy or within 8 weeks of its initiation; dialysis pericarditis—after being stabilized on dialysis (usually ≥8 weeks after its initiation)[153] and, very rarely, constrictive pericarditis. The global incidence of pericarditis in ESDR patients has declined to ∼5% in those patients starting dialysis.[152] The reported frequency of dialysis pericarditis ranges from 2 to 21%, but recent data are lacking.

Pericardial involvement in ESRD is manifested most commonly as acute pericarditis and chronic pericardial effusion and infrequently as chronic constrictive pericarditis. Typical features of this form of pericarditis include a lower rate of pleuritic chest pain (up to 30% of patients are asymptomatic) and the absence of ECG abnormalities in most cases, probably due to the lack of myocardial inflammation.[152–154] Patients with ESRD are more likely to develop chronic pericardial effusion due to continuous volume overload.[152] Not all pericardial effusions result from inflammation, and the normal volume of pericardial fluid is larger in stable haemodialysis patients than in normal controls.[155] With the advent of advanced renal replacement therapy, the incidence of haemodynamically significant effusions has decreased.[152,156,157] The most probable cause of uraemic pericarditis is the retention of toxic metabolites.[152,157] Since pericardial effusion is often bloody in uraemic patients, anticoagulation should be carefully considered or avoided in patients starting dialysis.[152,157]

5.4 Pericardial involvement in systemic autoimmune and autoinflammatory diseases

Pericardial involvement in systemic autoimmune diseases may be symptomatic (pericarditis and symptomatic pericardial effusion) or asymptomatic (usually pericardial effusion) and generally reflects the degree of activity of the underlying disease.[45] Approximately 5–15% of patients with acute or recurrent pericarditis may have a systemic autoimmune disease, either overt or underlying (*Table 1*, *Web Table 5*).[9,77,129–131] Pericardial involvement is common in systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis and scleroderma, but may also be present in systemic vasculitides, Behçet's syndrome, sarcoidosis and inflammatory bowel diseases. Pericardial involvement rarely occurs as the first manifestation of these diseases. In most patients the underlying disease has already been diagnosed by classical symptoms and signs. Concomitant myocardial inflammatory involvement may complicate the presentation and should be ruled out. If clinical features suggest a possible systemic autoimmune disease, a targeted aetiological search is warranted in cooperation with specialist consultation. The treatment is especially targeted at control of the systemic underlying disease.[45]

A specific subset of patients includes those with periodic fevers. These are genetic disorders characterized by mutations of genes involved in the regulation of the inflammatory response, without involvement of specific T cells or autoantibodies.[158–161] These disorders are usually detected in the paediatric population, although some patients experience disease onset during adulthood. The most

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common autoinflammatory syndromes include familial Mediterranean fever (FMF), in which serositis episodes last only 1–3 days, and tumour necrosis factor receptor-associated periodic syndrome (TRAPS), in which the episodes last for weeks. Mutations associated with these disorders are rare in recurrent pericarditis.[158–161] These conditions may be characterized by an exaggerated expression of IL-1.[161] A 10% rate of familial occurrence of pericarditis has been reported among the relatives of these patients.[162–164] These data suggest a genetic predisposition in at least a subset of patients; counselling may be warranted in these cases. A positive family history for pericarditis or periodic fevers, a poor response to colchicine, as well as the need for immunosuppressive agents are clues to the possible presence of an auto-inflammatory disease;[160] particularly in these conditions, anti-IL-1 or anti-TNF agents may be considered.[31,32,160]

5.5 Post-cardiac injury syndromes

The term post-cardiac injury syndromes (PCIS) is an umbrella term indicating a group of inflammatory pericardial syndromes including post-myocardial infarction pericarditis, post-pericardiotomy syndrome (PPS) and post-traumatic pericarditis (either iatrogenic or not).[132] Such syndromes are presumed to have an autoimmune pathogenesis triggered by initial damage to pericardial and/or pleural tissues caused by either myocardial necrosis (late post-myocardial infarction pericarditis or Dressler syndrome), surgical trauma (PPS), accidental thoracic trauma (traumatic pericarditis) or iatrogenic trauma with or without bleeding (pericarditis after invasive cardiac interventions).[131] The immune-mediated pathogenesis is supported by a latent period generally of a few weeks until the appearance of the first manifestations and the response to anti-inflammatory drugs (NSAIDs, corticosteroids, colchicine) with the possibility of recurrences. Pericardial bleeding and pleura incision are triggers for the syndrome.[165,166] Some forms, such as Dressler syndrome, have become rare with early reperfusion therapy of myocardial infarction; however, it may occur especially in cases of even minor bleeding into the pericardium.[167]

5.5.1 Definition and diagnosis

According to proposed diagnostic criteria for PPS,[168–170] the diagnosis of PCIS may be reached after a cardiac injury following clinical criteria: (i) fever without alternative causes, (ii) pericarditic or pleuritic chest pain, (iii) pericardial or pleural rubs, (iv) evidence of pericardial effusion and/or (v) pleural effusion with elevated CRP. At least two of five criteria should be fulfilled. The rationale for proposing specific criteria instead of adopting the same for pericarditis is that these syndromes may have concomitant pleuropericardial involvement and possible pulmonary infiltrates, and are not simply pericarditis.[170] Moreover, it is sometimes difficult to differentiate PCIS from the simple mechanical consequences of surgery (such as pericardial or pleural effusion). The demonstration of inflammatory activity should be essential to establish the diagnosis. Basic diagnostic evaluation of a patient with a suspected PCIS includes physical examination, ECG, echocardiogram, thoracic echography and/or chest X-ray.[132,165] On this basis, echocardiography is recommended when an iatrogenic complication is suspected after a cardiovascular intervention.[2,3,132]

5.5.2 Management

Treatment of PCIS is essentially based on empiric anti-inflammatory therapy, and may improve remission rates and reduce the risk of recurrences.[171] The same therapeutic scheme adopted for pericarditis is efficacious for all these forms, including post-myocardial infarction pericarditis (*Table 3*). Colchicine is not recommended for postoperative effusions in the absence of systemic inflammation.[172–174] Similarly NSAIDs are generally not indicated in asymptomatic post-surgical effusions, and this therapy may be associated with an increased risk of side effects related to NSAIDs.[173,174]

5.5.3 Prevention

Different preventive strategies have been examined in a few studies regarding aspirin,[175] methylprednisone,[176] dexamethasone[177] and colchicine.[168,169,172] Four controlled clinical trials for primary prevention of PPS were included in a systematic review on 894 patients; three studies were double-blind RCTs. Treatment comparisons were colchicine vs. placebo (two RCTs enrolling 471 patients), methylprednisolone vs. placebo (one RCT involving 246 paediatric patients) and aspirin vs. historical controls (one non-randomized study involving 177 paediatric patients). Meta-analytic pooling showed that only colchicine was associated with decreased risk of PPS [odds ratio (OR) 0.38]. Data on methylprednisolone (OR 1.13) and aspirin (OR 1.00) were negative.[178] The Colchicine for Prevention of the Post-pericardiotomy Syndrome and Postoperative Atrial Fibrillation (COPPS-2) trial confirmed the overall efficacy of perioperative use of colchicine, but it was also found to be associated with an increased risk of gastrointestinal side effects[172] compared with postoperative use of colchicine.[169] Colchicine is not recommended for the perioperative treatment and prevention of postoperative effusions in the absence of systemic inflammation.[172] In another trial,[177] high-dose dexamethasone (1 mg/kg as a single intraoperative dose) was not efficacious in preventing PPS or complicated PPS.

5.5.4 Prognosis

Despite limited published data, the prognosis of PPS is generally good.[178] There are very few available data on other forms of post-pericardial injury syndromes. In the largest published series on PPS patients after cardiac surgery,[166] complication rates were low: <4% for recurrences, <2% for cardiac tamponade and no cases of constriction, although hospital stay may be prolonged in these patients. However, the development of constrictive pericarditis has been reported in ~3% of cases.[36]

5.5.4.1 Post-myocardial infarction pericarditis

Following an acute myocardial infarction (AMI), three major pericardial complications may occur: (i) pericardial effusion, (ii) early infarct-associated pericarditis (often called early post-infarction pericarditis, typically a few days after AMI) and (iii) late pericarditis or post-cardiac injury (Dressler) syndrome (typically 1–2 weeks after AMI).

Early post-infarction pericarditis usually occurs soon after the AMI and is transient. This complication is rare in the primary percutaneous coronary intervention era and is especially related to late reperfusion or failed coronary reperfusion.[167] Diagnostic criteria do not differ from those for acute pericarditis. ECG changes are

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usually overshadowed by changes due to the myocardial infarction. However, ST segments may remain elevated, with persistence of upright T waves, as T waves may become upright again after having been inverted. Echocardiography should be performed in patients suspected of having post-AMI to evaluate for the presence of a pericardial effusion. CMR can be used to show the presence of concomitant pericardial inflammation.[179] Patients with a post-AMI pericardial effusion >10 mm in thickness should be investigated for a possible subacute rupture.[180,181] The treatment is generally supportive, as most cases are self-limited. However, a minority of patients may have persistent symptoms that require more than supportive care. For these patients, aspirin plus colchicine may be considered.

Late post-AMI pericarditis (Dressler syndrome) is rare (<1%) in the era of primary percutaneous coronary intervention and may reflect a larger size of AMI and/or late reperfusion.[167] Diagnosis and treatment are similar to that generally recommended for PCIS.

Although pericarditis is associated with a larger infarct size, in-hospital and 1-year mortality and major adverse cardiac events were similar in patients with and without pericarditis. Timely primary percutaneous coronary intervention may reduce the occurrence of post-AMI pericarditis. Early post-AMI pericarditis remains a marker of larger infarct size, but without independent prognostic significance.[167]

5.5.4.2 Postoperative effusions

Postoperative pericardial effusions are relatively common after cardiac surgery. They usually disappear in 7–10 days, but sometimes they persist for longer and can be dangerous. Early post-cardiac surgery pericardial collections must be interpreted in the clinical context of the patient. They have been reported as asymptomatic in 22% of patients 2 weeks after cardiac surgery.[182] The prognosis is good for mild effusions occurring in two of three cases, but moderate to large effusions (one of three) may progress to cardiac tamponade in ~10% of cases 1 month after cardiac surgery.[182,183] Treatment of these asymptomatic effusions by diclofenac was shown to be useless in the Post-Operative Pericardial Effusion (POPE) trial and may be associated with an increased risk of side effects related to NSAID use.[173] In contrast, cardiac tamponade occurring in the first hours after cardiac surgery is usually due to haemorrhage in the pericardial space, and surgical reintervention is mandatory in this situation.

Recommendations for the management and prevention of post-cardiac injury syndromes

Recommendations	Class[a]	Level[b]	Ref.[c]
Anti-inflammatory therapy is recommended in patients with PCIS to hasten symptom remission and reduce recurrences	I	B	171
Aspirin[d] is recommended as a first choice for anti-inflammatory therapy of post-myocardial infarction pericarditis and those patients already on antiplatelet therapies	I	C	
Colchicine added to aspirin or NSAIDs should be considered for the therapy of PCIS, as in acute pericarditis	IIa	B	58
Colchicine should be considered after cardiac surgery using weight-adjusted doses (i.e. 0.5 mg once for patients ≤70 kg and 0.5 mg twice daily for patients >70 kg) and without a loading dose for the prevention of PPS if there are no contraindications and it is tolerated. Preventive administration of colchicine is recommended for 1 month	IIa	A	168, 169
Careful follow-up after PCIS should be considered to exclude possible evolution towards constrictive pericarditis with echocardiography every 6–12 months according to clinical features and symptoms	IIa	C	

NSAIDs = non-steroidal anti-inflammatory drugs; PCIS = post-cardiac injury syndromes; PPS = post-pericardiotomy syndrome.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Antiplatelet effects of aspirin have been demonstrated for doses up to 1.5 g/day. There are no data for or against the use of higher doses in this setting.

5.6 Traumatic pericardial effusion and haemopericardium

Any cardiac intervention (e.g. percutaneous coronary intervention, pacemaker lead insertion, radiofrequency ablation) may be responsible for haemopericardium and cardiac tamponade due to coronary or cardiac chamber perforation. Pericardial effusion induced by trauma is included in the more expanded concept of PCIS.[132] However, in the event of overt chest trauma complicated by cardiac tamponade, the magnitude of the trauma is the main cause of the syndrome. Diagnosis includes the presence of a prior history of chest trauma as a trigger for the syndrome plus the signs and symptoms of pericarditis (i.e. chest pain, pericardial rub, dyspnoea, low-grade fever) and markers of inflammatory reaction (i.e. elevated CRP, leucocytosis, ESR). ECG is normally used to rule out AMI as a possible cause of pericarditis. Chest X-ray may help to detect cardiomegaly and pleural effusions. Transthoracic echocardiography is used to detect the presence, size and haemodynamic importance of the pericardial effusion. A recent randomized trial demonstrated that the use of limited transthoracic echocardiography improved the time from the trauma bay to the operating room and reduced the mortality rate.[184]

Therefore treatment differs according to the severity of the syndrome. For those with post-traumatic pericarditis with no haemodynamic compromise, treatment is essentially based on empirical anti-inflammatory therapy and adjunctive colchicine, which has been shown to be safe and efficacious for the prevention of pericarditis.[57] For those life-threatening cases of penetrating trauma to the heart and chest, emergency thoracotomy is recommended to improve survival as opposed to the classic strategy of initial

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pericardiocentesis as a bridge to surgery.[185,186] This is usually done through left anterolateral thoracotomy that makes pericardiotomy possible with effective relief of cardiac tamponade and direct cardiac massage if needed.

In the setting of aortic dissection with haemopericardium and suspicion of cardiac tamponade, emergency transthoracic echocardiography or a CT scan should be performed to confirm the diagnosis. In such a scenario, controlled pericardial drainage of very small amounts of the haemopericardium can be attempted to temporarily stabilize the patient in order to maintain blood pressure at ~90 mmHg.[187]

Recommendations for the management of traumatic pericardial effusion and haemopericardium in aortic dissection

Recommendations	Class[a]	Level[b]	Ref.[c]
Urgent imaging technique (transthoracic echocardiogram or CT) is indicated in patients with a history of chest trauma and systemic arterial hypotension	I	B	184
Immediate thoracotomy is indicated in cardiac tamponade due to penetrating trauma to the heart and chest	I	B	185
In the setting of aortic dissection with haemopericardium, controlled pericardial drainage of very small amounts of the haemopericardium should be considered to temporarily stabilize the patient in order to maintain blood pressure at about 90 mmHg	IIa	C	
Pericardiocentesis as a bridge to thoracotomy may be considered in cardiac tamponade due to penetrating trauma to the heart and chest	IIb	B	185

CT = computed tomography.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

5.7 Pericardial involvement in neoplastic disease

The differential diagnosis between malignant processes and other causes of pericarditis is particularly relevant and generally is accomplished by imaging, e.g. CT scan, cytology of pericardial fluid and eventually biopsies. Primary tumours of the pericardium, either benign (lipomas and fibromas) or malignant (mesotheliomas, angiosarcomas, fibrosarcomas), are very rare.[188,189] Mesothelioma, the most common malignant tumour, is almost always incurable. The most common secondary malignant tumours are lung cancer, breast cancer, malignant melanoma, lymphomas and leukaemias. Malignant pericardial effusions may be small, medium or large, with an imminent tamponade (frequent recurrences) or constriction; they may even be the initial sign of malignant disease.[190] The diagnosis is based on confirmation of the malignant infiltration within the pericardium.[188,189] Of note, in almost two-thirds of patients with documented malignancy, pericardial effusion is caused by non-malignant diseases, e.g. radiation pericarditis, other therapies or opportunistic infections.[189] Chest X-ray, CT, PET and CMR may reveal mediastinal widening, hilar masses and pleural effusion. Analyses of pericardial fluid and pericardial or epicardial biopsies are essential for the confirmation of malignant pericardial disease.[188–191]

The diagnostic yield of the concentrations of tumour markers in pericardial fluid remains controversial: carcinoembryonic antigen (CEA), CYFRA 21–1, neuron-specific enolase (NSE), CA-19–9, CA- 72–4, SCC, GATA3 and VEGF may be useful, but none of these tumour markers has been proven to be accurate enough for distinguishing malignant from benign effusions.[192,193] Epidermal growth factor receptor (EGFR) mutation should be evaluated and has prognostic indications in patients with malignant pericardial effusion in the course of lung adenocarcinoma[194] in order to tailor the treatment.

Treatment of cardiac tamponade is a class I indication for pericardiocentesis. The following steps are recommended in large suspected neoplastic pericardial effusion without tamponade: (i) systemic antineoplastic treatment as baseline therapy,[189] (ii) pericardiocentesis to relieve symptoms and establish a diagnosis and (iii) intrapericardial instillation of cytostatic/sclerosing agents to prevent recurrences. Pericardial drainage is recommended in all patients with large effusions because of the high recurrence rate (40–70%).[193–196] Prevention of recurrences may be achieved by intrapericardial instillation of sclerosing and cytotoxic agents.[197–204] Intrapericardial treatment should be tailored to the type of tumour: cisplatin was most effective in pericardial involvement in the course of lung cancer[200,204] and thiotepa was more effective in breast cancer pericardial metastases.[197,198] Tetracyclines as sclerosing agents also control malignant pericardial effusion in ~85% of cases, but side effects and complications are quite frequent: fever (19%), chest pain (20%) and atrial arrhythmias (10%).[189,199] Radiation therapy is very effective (93%) in controlling malignant pericardial effusion in patients with radiosensitive tumours such as lymphomas and leukaemias. However, radiotherapy of the heart can cause myocarditis and pericarditis.[189] Pericardiotomy is indicated when pericardiocentesis cannot be performed.[205] The procedure can be carried out under local anaesthesia, but complications include myocardial laceration, pneumothorax and mortality.[189,205] Surgical pericardiotomy does not improve clinical outcomes over pericardiocentesis and is associated with a higher rate of complications.[202] Pleuropericardiotomy allows drainage of malignant pericardial fluid into the pleural space. It is associated with a higher complication rate and offers no advantage over pericardiocentesis or pericardiotomy. Pericardiectomy is rarely indicated, mainly for pericardial constriction or complications of previous procedures.[189] Percutaneous balloon pericardiotomy creates a pleuropericardial direct communication, which allows fluid drainage into the pleural space: in large malignant pericardial effusions and recurrent tamponade it seems to be effective (90–97%) and safe.[204] Pericardial window creation via left minithoracotomy is a safe and effective approach in the surgical treatment of malignant cardiac

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tamponade.[205] In clinical practice, management is often palliative at late stages with advanced disease; it is aimed only at the relief of symptoms rather than treatment of the underlying disease, taking into account prognosis and the overall quality of life of the patients.[206]

Recommendations for the diagnosis and management of neoplastic involvement of the pericardium

Recommendations	Class[a]	Level[b]	Ref.[c]
Pericardiocentesis is recommended for cardiac tamponade to relieve symptoms and establish the diagnosis of malignant pericardial effusion	I	B	
Cytological analyses of pericardial fluid are recommended for the confirmation of malignant pericardial disease	I	B	191
Pericardial or epicardial biopsy should be considered for the confirmation of malignant pericardial disease	IIa	B	
Tumour marker testing should be considered for distinguishing malignant from benign effusions in pericardial fluid	IIa	B	193
Systemic antineoplastic treatment is recommended in confirmed cases of neoplastic aetiology	I	B	
Extended pericardial drainage is recommended in patients with suspected or definite neoplastic pericardial effusion in order to prevent effusion recurrence and provide intrapericardial therapy	I	B	
Intrapericardial instillation of cytostatic/sclerosing agents should be considered since it may prevent recurrences in patients with malignant pericardial effusion	IIa	B	197–204
Intrapericardial cisplatin should be considered in pericardial involvement in the course of lung cancer and intrapericardial instillation of thiotepa should be considered in breast cancer pericardial metastases	IIa	B	197, 198, 200, 204
Radiation therapy should be considered to control malignant pericardial effusion in patients with radiosensitive tumours such as lymphomas and leukaemias	IIa	B	
Pericardiotomy should be considered when pericardiocentesis cannot be performed	IIa	B	205
Percutaneous balloon pericardiotomy may be considered for the prevention of recurrences of neoplastic pericardial effusions	IIb	B	
Pericardial window creation via left minithoracotomy may be considered in the surgical treatment of malignant cardiac tamponade	IIb	B	207
Interventional techniques should consider seeding of neoplastic cells, patient prognosis and the overall quality of life of the patients	IIa	C	

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

5.8 Other forms of pericardial disease

5.8.1 Radiation pericarditis

Prior chest radiation is an important cause of pericardial disease. Most cases are secondary to radiation therapy for Hodgkin's lymphoma or breast or lung cancer. Serious radiation-induced pericardial disease was most often due to radiation therapy of Hodgkin's lymphoma, although the incidence of the condition has decreased with lower doses and modern radiation therapy techniques (shielding and dose calculation). As an example, the incidence of pericarditis decreased from 20 to 2.5%.[208] Less commonly, radiation exposure can cause other conditions (e.g. oesophageal cancer) or can occur in association with nuclear accidents. Soon after radiation the patient may develop acute pericarditis with or without effusion.[208] Late onset of pericardial disease is common; it has been observed in up to 20% of patients within 2 years following irradiation,[209] with a latency of up to 15–20 years, and is not necessarily preceded by acute pericarditis.[210] Late pericardial disease may consist of effusive-constrictive pericarditis or classical constrictive pericarditis (4–20% of patients) and appears to be dose dependent and related to the presence of pericardial effusion in the delayed acute phase.[209] Alternatively, radiation damage may result in a large pericardial effusion, with or without tamponade. The effusion may be serous or haemorrhagic and has a high probability of developing fibrous adhesions. Therapies are similar to those employed in pericarditis and pericardial effusion. Therapeutic radiation may cause other types of cardiac injury as well. The most serious is radiation-induced cardiomyopathy, but the coronary arteries and the cardiac valves may also be affected; this probably explains why pericardiectomy for radiation-induced disease is associated with a worse outcome than when performed for constrictive pericarditis resulting from most other causes.

Recommendations for the prevention and management of radiation pericarditis

Recommendations	Class[a]	Level[b]	Ref.[c]
Radiation therapy methods that reduce both the volume and the dose of cardiac irradiation are recommended whenever possible	I	C	

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Pericardiectomy should be considered for radiation-induced constrictive pericarditis, but with a worse outcome than when performed for constrictive pericarditis of other causes, because of co-existing myopathy	IIa	B	91,92, 103, 106

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

5.8.2 Chylopericardium

Chylopericardium is a pericardial effusion composed of chyle, the normal content of the lymphatic vessels. It is a rare disorder that may be primary or, more often, secondary to injury to the thoracic duct, which carries chyle from the intestinal tract to the blood at the junction of the left internal jugular and left subclavian veins.[211] It is often associated with chylothorax. Cardiac complications are cardiac tamponade, acute pericarditis and chronic constriction. Causes are trauma, surgery (especially for congenital heart disease), congenital lymphangiomatosis, radiotherapy, subclavian vein thrombosis, infection (e.g. TB), mediastinal neoplasms and acute pancreatitis.[212–214] Primary chylopericardium is less common and is a diagnosis by exclusion. CT with and without contrast enhancement or combined with lymphangiography/lymphangioscintigraphy (rarely performed) can be used to identify injury or blockage of the thoracic duct.

Chylopericardium should not be confused with cholesterol pericarditis, in which the fluid is clear and occurs in tuberculous pericarditis, rheumatoid pericarditis and trauma. The concentration of cholesterol equals or exceeds that of the blood. Pericardiocentesis is seldom effective and optimal therapy is radical pericardiectomy plus treatment of the underlying cause.[215,216]

Recommendations for the diagnosis and management of chylopericardium

Recommendations	Class[a]	Level[b]	Ref.[c]
Chylopericardium is diagnosed in the presence of a milky opalescent pericardial effusion, with a triglyceride level >500 mg/dl, cholesterol:triglyceride ratio <1, negative cultures and lymphocyte predominance (lymphocyte count between a few hundred to several thousand per millilitre)	I	C	
Pericardial drainage and parenteral nutrition should be considered in symptomatic or large uncontrolled effusion due to chylopericardium	IIa	C	
Surgical therapy should be considered for chylopericardium if conservative therapy does not reduce pericardial drainage and the course of the thoracic duct is identified	IIa	C	
Therapy with octreotide (100 μg s.c. × 3/day for 2 weeks) may be considered for chylopericardium (the mechanism of action is presumed to be a reduction in chyle production)	IIb	C	

s.c. = subcutaneous.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

5.8.3 Drug-related pericarditis and pericardial effusion

Pericardial reactions to drugs are rare (*Table 1*). Pericardial damage has also been associated with polymer fume inhalation, 'serum sickness' by blood products or foreign antisera, venoms (scorpion fish sting), foreign substance reactions by direct pericardial application (e.g. talc, magnesium silicate), silicones, tetracyclines, sclerosants, asbestos and iron in β-thalassaemia.[1] Management is based on discontinuation of the causative agent and symptomatic treatment.

The use of heparin and anticoagulant therapies is often perceived as a possible risk factor for the development of a worsening or haemorrhagic pericardial effusion that may result in cardiac tamponade, but a multivariable analysis of nearly 500 consecutive cases of acute pericarditis did not show this to be the case.[9] Similarly in another study of 274 patients with acute pericarditis or myopericarditis, the use of heparin or other anticoagulants was not associated with an increased risk of cardiac tamponade.[7] On the other hand, in the setting of iatrogenic pericardial effusion, full anticoagulation may be a risk factor for tamponade and complications.[217]

5.8.4 Pericardial effusion in metabolic and endocrine disorders

The main cause of pericardial diseases in this setting is represented by hypothyroidism. Pericardial effusion may occur in ~5–30% of patients with hypothyroidism, but recent data are lacking;[218,219] it may be quite large, but tamponade occurs rarely. It is diagnosed by a high thyroid stimulating hormone (TSH) level, and clinically is characterized by relative bradycardia and low QRS voltage in the ECG.

5.8.5 Pericardial involvement in pulmonary arterial hypertension

Pericardial effusion in the setting of pulmonary artery hypertension (PAH) is common (25–30%) and typically small in size, but rarely causes haemodynamic compromise. Pericardial effusion development in PAH appears to relate to right ventricular failure and a subsequent increase in right-sided filling pressures along with right atrial hypertension and increased pressure in the thebesian veins and coronary sinus. These processes result in increased filtration and lymphatic obstruction, resulting in pericardial effusion.[220]

Diagnosis of cardiac tamponade in a patient with severe PAH is challenging. Determining the haemodynamic significance of pericardial effusions in PAH requires increased attention since high right-sided pressures can mask many of the typical right-sided clinical and echocardiographic findings of tamponade. Because there is elevation in right-sided intracardiac chamber pressures, right-sided chamber collapse is uncommon. In contrast, left atrial pressure is

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typically lower in PAH and therefore left atrial early diastolic collapse is more commonly seen. Exaggerated ventricular interdependence, such as a decrease in left ventricular filling with early inspiration, may also be present.

The presence of pericardial effusion has been associated with connective tissue disease, shorter 6-minute walk distance and an elevated B-type natriuretic peptide level. Even a small quantity of excess pericardial fluid in a patient with PAH portends a poor prognosis. Pericardial effusions in PAH appear to be a marker of co-morbidity with either concomitant connective tissue disease or high venous pressure; these two factors are recognized to confer an adverse risk.[220]

5.8.6 Pericardial cysts

Pericardial cysts are rare mediastinal masses with an incidence of 1 in 100,000 patients[131,221] that have been described as diverticulae or cystic formations when an abnormal chest X-ray was obtained. They represent 6% of mediastinal masses and 33% of mediastinal cysts. Other cysts in the mediastinum are bronchogenic (34%), enteric (12%), thymic and others (21%).[131,221] They are often found in either one of the cardiophrenic angles.[131,206,221] Cysts do not communicate with the pericardial space, whereas diverticulae do. They may be uni- or multiloculated. Inflammatory cysts comprise pseudocyst as well as encapsulated or loculated pericardial effusions caused by rheumatic disorders, bacterial infection, trauma or cardiac surgery. Echinococcal cysts usually originate from ruptured hydatid cysts in the liver and the lungs. The differential diagnosis comprises loculated pericardial effusions of unknown origin and malignant pericardial masses. The diagnostic workup includes echocardiography, CT and eventually CMR to define the size, density and neighbouring structures.[131,221] They are mostly asymptomatic and detected incidentally, but can also present with chest discomfort, dyspnoea or palpitations due to cardiac compression. The first treatment for symptomatic congenital and inflammatory cysts is percutaneous aspiration,[206,222] possibly associated with ethanol sclerosis.[222] If the diagnosis is not completely established by imaging or the cyst recurs after drainage, surgical resection may be necessary. For echinococcal cysts, percutaneous aspiration and instillation of ethanol or silver nitrate after pre-treatment with albendazole (800 mg/day for 4 weeks) has been proposed.[1]

6. Age and gender issues in pericardial diseases

6.1 Paediatric setting

Pericarditis accounts for ~5% of all children who present with chest pain to a paediatric emergency department.[223] Children may be affected by the same syndromes that affect adults.[17] Diagnostic criteria are the same and the risk of recurrence is similar (15–30%). The aetiology is similar to that in adults, with PPS more often described, particularly after interatrial defect correction.[18] Compared with adults, children often have a marked inflammatory clinical pattern, with more commonly fever, pleuropulmonary involvement and raised CRP and less commonly anti-nuclear antibody (ANA) positivity. This might imply activation of inflammatory pathways with release of IL-1.[19]

No RCT has been done in children. NSAIDs remain the mainstay, at high dosages (*Web Table 7*). Most paediatricians avoid aspirin in children. Colchicine halved recurrences in children.[19] Corticosteroid use should be restricted in children even more than in adults, given that their side effects (striae rubre and growth impairment) are particularly deleterious in growing children; the minimal effective dose should be sought. Severe physical restriction is bothersome in children and may further worsen their quality of life and that of their family. Anakinra (anti-IL-1 receptor) is a new option for children, especially if they are corticosteroid-dependent.[20–23]

The long-term prognosis in children is good; however, quality of life can be severely affected with repeated recurrences, glucocorticoid dependence and severe physical restriction.[19]

Recommendations for therapy of acute and recurrent pericarditis in children

Recommendations	Class[a]	Level[b]	Ref.[c]
NSAIDs at high doses are recommended as first-line therapy for acute pericarditis in children until complete symptom resolution (see *Web Table 9* for dosages)	I	C	
Colchicine should be considered as an adjunct to anti-inflammatory therapy for acute recurrent pericarditis in children: <5 years, 0.5 mg/day; >5 years, 1.0–1.5 mg/day in two to three divided doses	IIa	C	
Anti-IL-1 drugs may be considered in children with recurrent pericarditis and especially when they are corticosteroid dependent	IIb	C	
Aspirin is not recommended in children due to the associated risk of Reye's syndrome and hepatotoxicity	III	C	
Corticosteroids are not recommended due to the severity of their side effects in growing children, unless there are specific indications such as autoimmune diseases	III	C	

IL = interleukin; NSAIDs = non-steroidal anti-inflammatory drugs.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

6.2 Pregnancy, lactation and reproductive issues

The most common form of pericardial involvement in pregnancy is hydropericardium, usually as a benign mild effusion by the third trimester, which is found in up to 40% of women, often occasionally. The effusion is usually silent and clinical examination and ECG are generally normal. In a few cases, slightly elevated blood pressure and/or aspecific ST-T changes have been documented.[24,25] The most common disease to require medical therapy is acute pericarditis; diagnosis is made using the usual criteria. No specific aetiology

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is usually identified. Nowadays the general outcomes of pregnancies in these women when followed by dedicated multidisciplinary teams are similar to those expected in the general population.[25]

A proposed treatment scheme for pericarditis during pregnancy is described in *Web Table 8*.[25–27] Pregnancy in women with recurrent pericarditis should be planned during a phase of disease quiescence.[25–27] Classic NSAIDs (ibuprofen, indomethacin) may be considered during the first and second trimesters;[25–27] most experts prefer high-dose aspirin, 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.[224,225] After gestational week 20, all NSAIDs (except aspirin $\leq$100 mg/day) can cause constriction of the ductus arteriosus and impair foetal renal function, and they should be withdrawn in any case at gestational week 32.[224,225] The lowest effective doses of prednisone may be used throughout pregnancy and breastfeeding (with supplementation with calcium and vitamin D).[25–27] Paracetamol is allowed throughout pregnancy and breastfeeding, as are anti-histamine H2 blockers or proton pump inhibitors.[226] During pregnancy, tapering of therapies should be extremely cautious. Normal vaginal delivery is possible and should be considered in the absence of contraindications.[25–27] Ibuprofen, indomethacin, naproxen and prednisone may be considered in women who are breastfeeding. After discontinuation of breastfeeding, gradual tapering of prednisone should be considered, eventually resuming colchicine. Colchicine is considered contraindicated during pregnancy and breastfeeding, even though no adverse events during pregnancy and foetal or child development have been reported in women with FMF treated with colchicine during pregnancy and breastfeeding.[227–229]

6.3 The elderly

Most guidelines have not discussed the applicability of their recommendations to older patients with multiple co-morbidities.[230] No paper has specifically addressed pericardial diseases in the elderly, so only expert opinion exists. Therapy adherence and compliance may be problematic in the elderly because of cognitive impairment, poor vision or hearing and cost, but the strongest predictor of non-adherence is the number of medications.[230] Indomethacin is not indicated, the colchicine dose should be halved and particular care should be taken to evaluate renal impairment and drug interactions.

7. Interventional techniques and surgery

The aetiology of pericardial diseases remains unresolved in many cases because the full spectrum of diagnostic methods is not used in many institutions. The gold standard remains surgical by the subxiphoid approach, allowing collection of fluid samples and performing pericardial biopsy and pericardial drainage. Interventional techniques[206] include the combined use of imaging by pericardioscopy first described in combination with diagnostic molecular, histological and immunohistological methods to assess the aetiology and pathogenesis of pericardial and epicardial disease manifestations[133] and the option to intervene therapeutically by instillation of drugs into the pericardial sac.[63,204]

7.1 Pericardiocentesis and pericardial drainage

For pericardial drainage and biopsy, the surgical approach remains the gold standard. The classical approach is by subxiphoid incision, through which it is easy to take fluid samples and perform a pericardial biopsy. The operation is completed by leaving a small drain in place to evacuate remaining effusion. This technique using a subxiphoid approach is straightforward for a thoracic or cardiovascular surgeon, if such a team is close to the cardiology team. In clinical practice, pericardial fluid is aspirated by pericardiocentesis.

State-of-the-art pericardiocentesis must be guided either by fluoroscopy or echocardiography[206] under local anaesthesia. Blind procedures must be not be used to avoid the risk of laceration of the heart or other organs, except in very rare situations that are immediately life threatening. An experienced operator and staff should perform pericardiocentesis in a facility equipped for radiographic, echocardiographic, haemodynamic and ECG monitoring.

For echo-guided pericardiocentesis, the ideal entry site is the point on the body surface where the effusion is closest to the transducer and the fluid collection is maximal. The needle trajectory is defined by the angulation of the handheld transducer and should avoid vital structures such as the liver, myocardium, lung, internal mammary artery (3–5 cm away from the parasternal border) and the vascular bundle at the inferior margin of each rib. The intended point of entry is marked on the skin and the direction of the ultrasound beam is carefully noted (see Web supplemental material). An additional technique is the echo-guided approach followed by echo-monitoring of the procedure.

For fluoroscopic-guided pericardiocentesis, a polytef-sheathed needle with an attached saline-filled syringe is advanced under moderate suction until the pericardial sac is reached.[206] When using the more common subxiphoid route for pericardiocentesis, a Tuohy-17, blunt-tip introducer needle is advanced to the left shoulder at a 30-degree angle to the skin, thus avoiding coronary, pericardial and internal mammary arteries. The lateral angiographic view provides the best visualization of the puncturing needle and its relation to the diaphragm and pericardium. The needle is slowly advanced towards the heart shadow and the epicardial halo phenomenon, under moderate suction and with injection of small amounts of diluted contrast medium, until pericardial fluid is aspirated. If haemorrhagic fluid is freely aspirated, a few millilitres of contrast medium may be injected under fluoroscopic control to verify the position of the needle. A soft J-tip guidewire is then introduced and after dilatation is exchanged for a multihole pigtail catheter, through which the fluid is evacuated under the control of intrapericardial pressure.[206]

Pericardiocentesis should be performed by experienced operators and carries a risk of complications ranging from 4 to 10% depending on the type of monitoring, the skill of the operator and the setting (emergency vs. urgent vs. elective).[183,206] Most common complications include arrhythmias, coronary artery or cardiac chamber puncture, haemothorax, pneumothorax, pneumopericardium and hepatic injury (*Web Table 9*).

Pericardiocentesis may have additional limitations/dangers when pericardial fluid is not free and when located in a lateral or posterior position or $<$10 mm. In these cases a surgical approach might be safer, depending on local expertise and availability.

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7.2 Pericardioscopy

Pericardioscopy permits visualization of the pericardial sac with its epicardial and pericardial layers. Macroscopic views show a clustering of protrusions, haemorrhagic areas and neovascularization in malignant pericardial effusion, which are often haemorrhagic, in contrast to radiogenic or viral and autoimmune effusions.[133,206]

Pericardioscopy enables the performing physician to take targeted biopsy specimens from epicardial and pericardial layers, avoiding epicardial vessels and increasing the probability of obtaining disease-specific results. For safety reasons it is important to have a second wire in place. The safety wire allows a quick exchange with a pigtail catheter and allows autotransfusion in the case of relevant bleeding. By selecting the biopsy site, less informative white areas of fibrin can be avoided and dark spots of inflammation, malignancy or haemorrhagic imbibitions can be selected, which can be identified best in the blue-light mode. Pericardial biopsy can even be taken under radiologic control alone. The open jaws of the bioptome are advanced gently until the silhouette of the pericardial sac is reached. Then the jaws are closed and the biopsy sample is taken. Seven to 10 samples should be taken to reduce sampling error. The most meaningful diagnostic yield from pericardial biopsies can be obtained by multiple pericardioscopically guided tissue acquisitions.

This technique is quite demanding and can be performed in only a limited number of experienced tertiary referral centres. Pericardioscopy may be considered as a diagnostic method for inspection of the pericardium and epicardium in experienced centres. It permits safe tissue acquisition in pericardial diseases of unknown origin.

7.3 Pericardial fluid analysis, pericardial and epicardial biopsy

Serosanguinous or haemorrhagic fluid can be found in malignant as well as post-pericardiotomy, rheumatologic and traumatic effusions or can be caused by iatrogenic lesions during pericardiocentesis, but also in idiopathic and viral forms. In cases of sepsis, TB or in HIV-positive patients, bacterial cultures can be diagnostic. Fluid cytology can separate malignant from non-malignant effusions, which is important for effusions in tumour patients after radiotherapy of the mediastinum. Discriminative signatures between malignant and autoreactive effusions are higher levels of tumour markers in neoplastic pericardial effusion.[133,206]

Cytology and assessment of bacterial cultures of the fluid, histological/immunohistological evaluation of biopsy specimens and molecular analysis (PCR for microbial agents of fluid and tissue) allow a definite aetiological diagnosis in many cases, which permits further treatment.[133]

7.4 Intrapericardial treatment

In patients with a larger effusion of unknown origin, prolonged pericardial drainage may allow subsequent intrapericardial treatment.

In neoplastic pericardial effusion, most frequently due to bronchus carcinoma or breast cancer, intrapericardial cisplatin or thiotepa therapy have been proposed in combination with systemic antineoplastic treatment, which should be tailored in collaboration with the oncologist.[204]

In autoreactive and lymphocytic pericardial effusion disease-specific intrapericardial crystalloid triamcinolone (300 mg/m^2 body surface) may be considered.[64] Viral pericarditis may be excluded by PCR in fluid and tissue specimens, but such investigations are not usually performed in uncomplicated cases in clinical practice.

In cases of uraemic pericardial effusion, intrapericardial therapy with triamcinolone may be considered, apart from intensified haemo- or peritoneal dialysis and fluid evacuation.[64,65]

In rare cases of recurrent effusion, balloon pericardiotomy is an option that allows a (transient) pericardio(-pleural-)abdominal window for drainage. This approach should be avoided in neoplastic or purulent effusions.

7.5 Pericardial access for electrophysiology

First reported in 1996,[231] pericardial access has been used for the mapping and ablation of epicardial substrates of ventricular tachyarrhythmias with improved success rates and avoidance of a surgical procedure[232,233] (see supplemental Web material and *Web Table 9* for complications of the procedure).

7.6 Surgery for pericardial diseases

7.6.1 Pericardial window

A pericardial window is a cardiac surgical procedure to create a communication, or 'window', from the pericardial space to the pleural cavity. The purpose of the window is to allow a pericardial effusion (usually malignant) to drain from the space surrounding the heart into the chest cavity in order to prevent a large pericardial effusion and cardiac tamponade.

The window is usually performed by a cardiac surgeon, but a pericardial window may be created by video-assisted thoracoscopy or balloon pericardiotomy by a percutaneous intervention. The main indication is represented by recurrent large effusions or cardiac tamponade when a more complex operation such pericardiectomy is a high risk or the life expectancy of the patient is reduced (e.g. neoplastic pericardial disease) and the intervention is palliative. The results of a pericardial window are less definitive since the communication may close and recurrent effusions, especially loculated, are common and may require additional interventions compared with pericardiectomy, which is a more complex but complete operation.[105]

7.6.2 Pericardiectomy

In constrictive pericarditis the treatment is pericardectomy. The decortications should remove as much of the pericardium as possible with all constricting parietal and epicardial layers,[103–105] but taking care of perserving the phrenic nerves bilaterally. Only by using sternotomy can all the constricting pericardial layers be removed. Therefore, left anterolateral thoracotomy should be avoided since it permits only a partial resection.

It is also necessary to liberate all of the right atrium, the superior vena cava and especially the inferior vena cava and the inferior part of the right ventricle adjacent to the diaphragm as far as possible.[103–105] Only when the constricting peel is adherent and calcified is it necessary to leave behind a few islands of the pericardium. To avoid bleeding, cardiopulmonary bypass should be employed only in cases of co-existent cardiac surgical lesions, but cardiopulmonary bypass may be needed in stand-by, in case of the occurrence of haemorrhagic lesions during the procedure. By

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applying these principles, the controversy over the type of operation (complete or radical or only anterior pericardiectomy) is not an issue. In recurrent constrictive pericarditis, a repeated operation has to be done as soon as possible, ideally during the first postoperative year. Rare patients with relapsing pericarditis can also benefit from pericardiectomy.[33]

8. Perspective and unmet needs

Despite a large amount of new data and the first clinical trials that allow clinical management to be on the road to evidence-based medicine, there are several issues that require additional research and clarification. The main issues and unsolved questions include

(1) Pathophysiology and risk factors for recurrent pericarditis. What is really 'idiopathic recurrent pericarditis'?
(2) How is it possible to prevent pericarditis beyond colchicine?
(3) Is drug tapering useful for patients with pericarditis?
(4) What is the best treatment duration for patients with pericardial diseases?
(5) New and individualized therapies for refractory recurrent pericarditis. Are they really available and useful?
(6) Is exercise restriction really needed for patients with acute and recurrent pericarditis?
(7) Given the high risk of constrictive pericarditis in infective pericarditis (i.e. tuberculous and purulent) and the promising effect of intrapericardial fibrinolysis in case reports and small trials, is intrapericardial fibrinolysis in exudative pericarditis really safe and efficacious? And when should it be considered in the clinical management of patients?
(8) What interventions are required to reduce the high mortality of tuberculous pericarditis treated with antituberculosis medication?
(9) What actually is pericarditis with myocarditis?
(10) What are the long-term outcomes of patients with myopericarditis and perimyocarditis?
(11) Aetiology and pathophysiology of isolated pericardial effusion. What is 'idiopathic pericardial effusion'?
(12) Is diagnosis and treatment necessary for all moderate to large pericardial effusions?
(13) What are the indications for invasive diagnostic techniques and their diagnostic yield in clinical practice?
(14) What is the role, value and application of intrapericardial therapies?
(15) Is pericardiectomy really useful and indicated in refractory recurrent pericarditis?
(16) What are the causes and risk factors for constrictive pericarditis?
(17) What is the best timing for surgical therapies in pericardial diseases?

Ongoing basic and clinical research is warranted and needed to address all these issues and provide additional diagnostic and therapeutic tools for individualized management of each patient and to improve the prognosis.

9. To do and not to do messages from the pericardium guidelines

Management of acute and recurrent pericarditis	Class[a]	Level[b]
Hospital admission is recommended for high-risk patients* with acute pericarditis	I	B
Colchicine use (0.5 mg twice or once daily for patients <70 kg or intolerant to higher doses) is recommended as first-line therapy for acute pericarditis as an adjunct to aspirin/NSAIDs therapy (3 months) and is also recommended for recurrent pericarditis (6 months)	I	A
Corticosteroids are not recommended as first-line therapy for acute pericarditis	III	C
CRP should be considered to guide the treatment duration and assess the response to therapy	IIa	C
Recommendation for management and therapy of pericardial effusion		
Pericardiocentesis or cardiac surgery is indicated for cardiac tamponade or for symptomatic moderate to large pericardial effusions not responsive to medical therapy and for suspicion of unknown bacterial or neoplastic aetiology	I	C
A triage of patients with pericardial effusion is recommended (see *Figure 3*)	I	C
It is recommended to target the therapy of pericardial effusion according to the aetiology	I	C
Recommendation for diagnosis and therapy of constrictive pericarditis		
CT and/or CMR are indicated as second-level imaging techniques (after echocardiography and chest X-ray) to assess calcifications (CT), pericardial thickness, degree and extension of pericardial involvement	I	C
Cardiac catheterization is indicated when non-invasive diagnostic methods do not provide a definite diagnosis of constriction	I	C
The mainstay of treatment of chronic permanent constriction is pericardiectomy	I	C
Recommendation for diagnostic work-up of pericardial diseases		
In all cases of suspected pericardial disease first diagnostic evaluation is recommended, with auscultation, ECG, transthoracic echocardiography, chest X-ray and routine blood tests, including markers of inflammation (i.e. CRP and/or ESR), WBC count with differential, renal function, liver tests and myocardial damage (creatine kinase, troponin)	I	C
CT and/or CMR are second-level testing for diagnostic workup in pericarditis	I	C
Further testing is indicated in high-risk patients* according to the clinical conditions	I	C

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Management of tuberculous pericarditis and effusion		
In patients living in endemic areas, empiric anti-TB chemotherapy is recommended for exudative pericardial effusion, after excluding other causes	I	C
In patients living in non-endemic areas, empiric anti-TB treatment is not recommended when systematic investigation fails to yield a diagnosis of tuberculous pericarditis	III	C
Standard anti-TB drugs for 6 months is recommended for the prevention of tuberculous pericardial constriction	I	C
Pericardiectomy is recommended if the patient's condition is not improving or is deteriorating after 4–8 weeks of antituberculosis therapy	I	C
Management of neoplastic pericardial disease		
Cytological analyses of pericardial fluid are recommended for the confirmation of malignant pericardial disease	I	B
Pericardial or epicardial biopsy should be considered for the confirmation of malignant pericardial disease	IIa	B
Tumour marker testing should be considered for distinguishing malignant from benign effusions in pericardial fluid	IIa	B
Systemic antineoplastic treatment is recommended in confirmed cases of neoplastic aetiology	I	B
Extended pericardial drainage is recommended in patients with suspected or definite neoplastic pericardial effusion in order to prevent effusion recurrence and provide intrapericardial therapy	I	B
Intrapericardial instillation of cytostatic/sclerosing agents should be considered since it may prevent recurrences in patients with malignant pericardial effusion	IIa	B

CMR = cardiac magnetic resonance; CRP = C-reactive protein; CT = computed tomography; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; NSAID = non-steroidal anti-inflammatory drug; TB = tuberculosis; WBC = white blood cell.
*High risk when there is at least one risk factor among the following: high fever (>38°C), subacute course without a clear-cut acute onset, large pericardial effusion (i.e. diastolic echo-free space >20 mm), cardiac tamponade, failure to respond to NSAID therapy, myopericarditis, immunodepression, trauma or oral anticoagulant therapy.
[a]Class of recommendation.
[b]Level of evidence.

10. Web addenda

All Web figures and Web tables are available in the online addenda at: http://www.escardio.org/Guidelines-&-Education/Clinical-Practice-Guidelines/Pericardial-Diseases-Guidelines-on-the-Diagnosis-and-Management-of

11. Appendix

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