Complete Summary

GUIDELINE TITLE

Guidelines on the diagnosis and management of pericardial diseases. The task force on the diagnosis and management of pericardial diseases of the European Society of Cardiology.

BIBLIOGRAPHIC SOURCE(S)

Maisch B, Seferovic PM, Ristic AD, Erbel R, Rienmuller R, Adler Y, Tomkowski WZ, Thiene G, Yacoub MH. Guidelines on the diagnosis and management of pericardial diseases. Sophia Antipolis (FR): European Society of Cardiology; 2004. 28 p. [275 references]

GUIDELINE STATUS

This is the current release of the guideline.

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s)/intervention(s) for which important revised regulatory information has been released.

- February 28, 2008, Heparin Sodium Injection: The U.S. Food and Drug Administration (FDA) informed the public that Baxter Healthcare Corporation has voluntarily recalled all of their multi-dose and single-use vials of heparin sodium for injection and their heparin lock flush solutions. Alternate heparin manufacturers are expected to be able to increase heparin production sufficiently to supply the U.S. market. There have been reports of serious adverse events including allergic or hypersensitivity-type reactions, with symptoms of oral swelling, nausea, vomiting, sweating, shortness of breath, and cases of severe hypotension.
- June 8, 2007, Troponin-I Immunoassay: Class I Recall of all lots of the Architect Stat Troponin-I Immunoassay. The assay may report falsely elevated or falsely decreased results at and near a low level, which may impact patient treatment.
- May 2, 2007, Colchicine: Immediate drug recall for all strengths, sizes and lots of ApothéCure compounded injectable Colchicine sold within the last year due to recent deaths associated with the use of the product.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Pericardial diseases, including congenital defects, pericarditis (dry, effusive, effusive-constrictive, and constrictive), neoplasms, and cysts

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Cardiology
Family Practice
Internal Medicine
Surgery

INTENDED USERS

Hospitals
Physicians

GUIDELINE OBJECTIVE(S)

To provide recommendations on the diagnosis and management of patients with pericardial diseases

TARGET POPULATION

Patients with pericardial diseases

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Auscultation
2. Chest x-ray
3. Echocardiography including transoesophageal and 2-D Doppler echocardiography
4. Computed tomography (CT) scan
5. Magnetic resonance imaging (MRI, including spin-echo and cine MRI)
6. Electrocardiography
7. Determination of pulsus paradoxus
8. Blood analyses including erythrocyte sedimentation rate (ESR), C-reactive peptide (CRP), lactate dehydrogenase (LDH), leukocytes, troponin I, creatine kinase-muscle band (CK-MB)
9. Pericardioscopy
10. Cardiac catheterisation
11. Angiography
12. Epicardial and pericardial biopsy (including polymerase chain reaction, immunocytochemistry, and immunohistochemistry)
13. Serum antibody levels
14. Gram, acid-fast, and fungal staining
15. Cultures of the pericardial and body fluids

Treatment/Management

1. Nonsteroidal anti-inflammatory drugs (NSAID) including ibuprofen
2. Aspirin
3. Colchicine
4. Corticosteroids (including prednisone and triamcinolone)
5. Azathioprine
6. Cyclophosphamide
7. Fluid substitution
8. Catecholamines
9. Digitalis
10. Albendazole
11. Percutaneous aspiration and instillation of ethanol or silver nitrate
12. Hyperimmunoglobulin
13. Interferon alpha
14. Immunoglobulin
15. Antibiotics including antistaphylococcal antibiotics, gentamycin, tetracycline, doxycycline, minocycline, bleomycin, penicillin, and sulfonamides
16. Urokinase or streptokinase
17. Antituberculous drugs
18. Peritoneal dialysis
19. Haemodialysis
20. Radionuclides
21. Antifungal agents including fluconazole, ketoconasole, itraconasole, amphotericin B, liposomal amphotericin B, and amphotericin B lipid complex
22. Systemic antineoplastic treatment including cisplatin and thiotepa
23. Pericardiocentesis
24. Pleuropericardial fenestration
25. Percutaneous balloon pericardiotomy

26. Pericardiectomy including antero-lateral thoracotomy (fifth intercostals space) and median sternotomy (faster access to the aorta and right atrium for extra-corporeal circulation)

MAJOR OUTCOMES CONSIDERED

- Signs and symptoms of pericardial diseases
- Cardiac morbidity and mortality
- Sensitivity and specificity of diagnostic tests

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Patient Registry Data
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

423

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

A: Data derived from multiple randomised clinical trials or meta-analyses

B: Data derived from a single randomised trial or nonrandomised studies

C: Consensus opinion of the experts and/or small studies

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review by a subgroup of the task force, then presentation to the entire task force to reach consensus.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Formulation of drafts in specific areas by a subgroup of the task force, then presentation to the entire task force to reach consensus.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Indications for various tests and procedures were ranked in three classes:

Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment

- **Class IIa**: Weight of evidence/opinion is in favour of usefulness/efficacy.
- **Class IIb**: Usefulness/efficacy is less well established by evidence/opinion.

Class III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

A review coordinator is appointed with the Committee for Practice Guidelines (CPG). The document is reviewed by the members of the CPG, the European Society of Cardiology Board Members, and other experts in the field chosen from joint societies, working groups, and other sources.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The class of recommendations (I-III) and level of evidence (A-C) are defined at the end of the "Major Recommendations" field.

Pericardial syndromes

Congenital defects of the pericardium

Congenital defects of the pericardium (1/10,000 autopsies) comprise partial left (70%), right (17%), or total bilateral (extremely rare) pericardial absence. About 30% of patients have additional congenital abnormalities. Most patients with a total absence of pericardium are asymptomatic. However, homolateral cardiac displacement and augmented heart mobility impose an increased risk for traumatic aortic type A dissection. Partial left side defects can be complicated by cardiac strangulation caused by herniation of the left atrial appendage, atrium, or left ventricle through the defect (chest pain, shortness of breath, syncope, or sudden death). The chest x-ray is typical, but the diagnosis is confirmed by echocardiography and computed tomography (CT)/magnetic resonance imaging (MRI). Excision of the atrial appendage and surgical pericardioplasty (Dacron, Gore-tex, or bovine pericardium) is indicated for imminent strangulation.

Acute pericarditis

Acute pericarditis is either dry, fibrinous, or effusive, independent from its aetiology (please refer to table 1 of the original guideline document for information on the aetiology, incidence, and pathogenesis of pericarditis). A prodrome of fever (usually <39 degrees C), malaise, and myalgia is common, but elderly patients may not be febrile. Major symptoms are retrosternal or left precordial chest pain (radiates to the trapezius ridge, can be pleuritic or simulate ischaemia, and varies with posture), nonproductive cough, and shortness of breath. The pericardial friction rub can be transient, mono-, bi- or triphasic. Pleural effusion may be present. Pericarditis is often accompanied by some degree of myocarditis (evidenced by global or regional myocardial dysfunction, myalgias, or rhabdomyolysis, elevations of troponins I and T, muscle band [MB] creatine-kinase, serum myoglobin levels, and tumour necrosis factor). Auscultation of a new S3 heart sound, convexly elevated J-ST segment in the electrocardiogram (ECG), fixation of Indium-111-labelled antimyosin antibodies, and structural changes in MRI are indicative. However, only endomyocardial/epimyocardial biopsy findings are diagnostic.

The diagnostic algorithm can be derived from Table 2 of the original guideline document (see below). Heart rate is usually rapid and regular. Microvoltage and electrical alternans are reversible after effusion drainage. Findings by chest x-ray, CT, and MRI are shown in Table 3 of the original guideline document. Echocardiography is essential to detect pericardial effusion and to check for concomitant heart disease or paracardial pathology.

Table 2: Diagnostic pathway and sequence of performance in acute pericarditis (level of evidence B for all procedures)

Technique	Characteristic findings	Reference

Technique	Characteristic findings	Reference
Obligatory (class I)		
Auscultation	Pericardial rub (mono-, bi-, or triphasic)	Spodick,1997
Electrocardiography (ECG)[a]	Stage I: anterior and inferior concave ST segment elevation. PR segment deviations opposite to P polarity. Early stage II: ST junctions return to the baseline, PR deviated. Late stage II: T waves progressively flatten and invert Stage III: generalised T wave inversions Stage IV: ECG returns to prepericarditis state.	Spodick, 2001
Echocardiography	Effusion types B-D (Horowitz) (Fig. 1 in original guideline document) Signs of tamponade (see Section 3.5)	Levine et al., 1991; Chuttani et al, 1991
Blood analyses	(a) Erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), lactate dehydrogenase (LDH), leukocytes (inflammation markers) (b) Troponin I, CK-MB (markers of myocardial lesion)[b]	Meyers, Meyers, & Prendergast, 1997
Chest x-ray	Ranging from normal to "water bottle" heart shadow. Revealing additional pulmonary/mediastinal pathology.	Eisenberg et al., 1993
Mandatory in tamponade (class I), optional in large/recurrent effusions or if previous tests inconclusive (class IIa) in small effusions (class IIb)		
Pericardiocentesis and drainage	Polymerase chain reaction (PCR) and histochemistry for	Maisch, Ristić, & Pankuweit, 2002;

Technique	Characteristic findings	Reference
	aetiopathogenetic classification of infection or neoplasia	Maisch et al., 1994; Tsang et al., 2002
Optional or if previous tests inconclusive (class IIa)		
CT	Effusions, peri-, and epicardium	Chiles et al., 2001
MRI	Effusions, peri-, and epicardium	Chiles et al., 2001
Pericardioscopy, pericardial biopsy	Establishing the specific aetiology	Maisch, Ristić, & Pankuweit, 2002; Maisch et al., 1994; Nugue et al., 1996; Seferović et al., 2003

[a]Typical lead involvement: I, II, aVL, aVF, and V3-V6. The ST segment is always depressed in aVR, frequently in V1, and occasionally in V2. Occasionally, stage IV does not occur and there are permanent T wave inversions and flattenings. If ECG is first recorded in stage III, pericarditis cannot be differentiated by ECG from diffuse myocardial injury, "biventricular strain," or myocarditis. ECG in EARLY REPOLARIZATION is very similar to stage I. Unlike stage I, this ECG does not acutely evolve and J-point elevations are usually accompanied by a slur, oscillation, or notch at the end of the QRS just before and including the J point (best seen with tall R and T waves – large in early repolarisation pattern). Pericarditis is likely if in lead V6 the J point is >25% of the height of the T wave apex (using the PR segment as a baseline).

[b] Cardiac troponin I was detectable in 49% and >1.5 ng/ml in 22% of 69 patients with acute pericarditis (only in those with ST elevation in ECG) investigated by Bonnefoy et al. (2000) In another study (Brandt, Filzmaier, & Hanrath, 2001), troponin I was detected in 10/14 patients with a median peak concentration of 21.4 mg/mL (range 0.5 to >50 ng/ml). CK-MB was elevated in 8/14 patients with the median peak of 21 U/L (range 13 to 43), corresponding to the relative index of 10.2% of the total CK activity.

Hospitalisation is warranted for most patients to determine the aetiology, observe for tamponade, and start anti-inflammatory and symptomatic treatment. Nonsteroidal anti-inflammatory drugs (NSAID) are the mainstay (level of evidence B, class I). Ibuprofen is preferred for its rare side effects, favourable effect on the coronary flow, and the large dose range. Depending on severity and response, 300 to 800 mg every 6 to 8 h may be initially required and can be continued for days or weeks, best until the effusion has disappeared. Gastrointestinal protection must be provided in all patients. Colchicine (0.5 mg twice a day [bid]) added to an NSAID or as monotherapy also appears to be effective for the initial attack and the prevention of recurrences (level of evidence B, class IIa). It is well tolerated with fewer side effects than NSAIDs. Systemic corticosteroid therapy should be restricted to connective tissue diseases, autoreactive or uremic pericarditis. Intrapericardial application avoids systemic side effects and is highly effective (level of evidence B, class IIa). For tapering of prednisone, ibuprofen or colchicine should be introduced early (level of evidence B, class IIa). Recovered patients should be observed for recurrences or constriction. If patients require anticoagulants, heparin is recommended under strict observation. Pericardiocentesis is indicated for clinical tamponade, high suspicion of purulent or

neoplastic pericarditis (level of evidence B, class I), or for large or symptomatic effusions despite the medical treatment for more than one week (Please see below and refer to focus box 1 of the original guideline document for information on pericardiocentesis).

Focus box 1: pericardiocentesis

Pericardiocentesis is life saving in cardiac tamponade (level of evidence B, class I). Aortic dissection is a major contraindication. Relative contraindications include uncorrected coagulopathy; anticoagulant therapy; thrombocytopenia <50,000/mm^3; and small, posterior, and loculated effusions. Pericardiocentesis in acute traumatic haemopericardium and purulent pericarditis is probably less appropriate than surgical drainage. In effusions causing no haemodynamic compromise, pericardiocentesis is indicated in effusions >20 mm in echocardiography in diastole or for diagnostic purposes if additional procedures are available (e.g., pericardial fluid and tissue analyses, pericardioscopy, and epicardial/pericardial biopsy) which could reveal the etiology of the disease and permit further causative therapy (level of evidence B, class IIa).

Pericardiocentesis guided by fluoroscopy is performed in the cardiac catheterisation laboratory with ECG monitoring. Direct ECG monitoring from the puncturing needle is not an adequate safeguard. Right-heart catheterization can be performed simultaneously with pericardiocentesis, allowing monitoring the improvement as the effusion is drained. The subxiphoid approach has been used most commonly, with a long needle with a mandrel (Tuohy or thin-walled 18-gauge) directed towards the left shoulder at a 30 degree angle to the skin. This route is extrapleural and avoids the coronary, pericardial, and internal mammary arteries. The operator intermittently attempts to aspirate fluid and injects small amounts of contrast. If haemorrhagic fluid is freely aspirated, a few millilitres of contrast medium may be injected under fluoroscopic observation. The appearance of sluggish layering of contrast medium inferiorly indicates that the needle is correctly positioned. A soft J-tip guidewire is introduced and, after dilatation, exchanged for a multi-holed pigtail catheter. It is prudent to drain the fluid in steps of less than 1L at a time to avoid the acute right-ventricular dilatation ("sudden decompression syndrome"). It is essential to check the position of the guidewire in at least two angiographic projections. If the guidewire was erroneously placed intracardially, this should be recognized before insertion of the dilator and drainage catheter. If, despite the caution, the introducer set or the catheter have perforated the heart and are laying intracardially, the catheter should be secured and the patient promptly transferred to the cardiac surgery. Alternatively, a second puncture can be attempted. If successful, surgery may be avoided using autotransfusion of pericardial blood.

Echocardiographic guidance of pericardiocentesis is technically less demanding and can be performed in the intensive care unit at the bedside. Echocardiography should identify the shortest route where the pericardium can be entered intercostally (usually in the sixth or seventh rib space in the anterior axillary line). Prolonged pericardial drainage is performed until the volume of effusion obtained by intermittent pericardial aspiration (every 4 to 6 h) fall to <25 mL per day.

The feasibility is high (93%) in patients with anterior effusion $\geq$10 mm, while the rate of success is only 58% with small, posteriorly located effusions. Fluoroscopic

and haemodynamic monitoring improve feasibility (93.1% vs. 73.3%) in comparison to emergency pericardial puncture with no imaging control. The tangential approach using the epicardial halo phenomenon in the lateral view significantly increased the feasibility of fluoroscopically guided pericardiocentesis in patients with small effusions (200 to 300 mL) (92.6% vs. 84.9%) and very small effusions (<200 mL) (89.3% vs. 76.7%). Pericardiocentesis with echocardiography guidance was feasible in 96% of loculated pericardial effusions after cardiac surgery. A rescue pericardiocentesis guided by echocardiography successfully relieved tamponade after cardiac perforation in 99% of 88 patients and was the definitive therapy in 82% of the cases. The most serious complications of pericardiocentesis are laceration and perforation of the myocardium and the coronary vessels. In addition, patients can experience air embolism, pneumothorax, arrhythmias (usually vasovagal bradycardia), and puncture of the peritoneal cavity or abdominal viscera. Internal mammary artery fistulas, acute pulmonary oedema, and purulent pericarditis were rarely reported. The safety was improved with echocardiographic or fluoroscopic guidance. Recent large echocardiographic series reported an incidence of major complications of 1.3 to 1.6%. In a large series of fluoroscopy-guided percutaneous pericardiocenteses, cardiac perforations occurred in 0.9%, serious arrhythmias in 0.6%, arterial bleeding in 1.1%, pneumothorax in 0.6%, infection in 0.3%, and a major vagal reaction in 0.3%. Incidence of major complications was further significantly reduced by utilizing the epicardial halo phenomenon for fluoroscopic guidance.

Chronic pericarditis

Chronic pericardial inflammation (>3 months) includes effusive, adhesive, and constrictive forms. It is important to differentiate chronic inflammatory effusions from noninflammatory hydropericardium (congestive heart failure). Symptoms are usually mild (chest pain, palpitations, fatigue), related to the degree of chronic cardiac compression and residual pericardial inflammation.

The diagnostic algorithm is similar as in acute pericarditis (see above and Table 2 of the original guideline document). The detection of the curable causes (e.g., tuberculosis, toxoplasmosis, myxedema, autoimmune, and systemic diseases) allows specific therapy with high success rate. Symptomatic treatment is as in acute pericarditis. Intrapericardial instillation of crystalloid nonabsorbable corticosteroids is highly efficient in autoreactive forms. Pericardiocentesis is indicated as a diagnostic and therapeutic procedure. If the recurrences are frequent, pleuropericardial fenestration and percutaneous balloon pericardiotomy may be appropriate (level of evidence B, class IIb). For chronic persistent/recurrent large effusions despite intrapericardial therapy or balloon pericardiotomy, pericardiectomy should be considered.

Recurrent pericarditis

The term recurrent pericarditis encompasses (1) the intermittent type (widely varying symptom-free interval without therapy) and (2) the incessant type (discontinuation of anti-inflammatory therapy always ensures a relapse). Mechanisms suggested to explain recurrence include (1) insufficient dose or/and insufficient treatment duration of antiphlogistics or corticoids in an autoimmune pericardial disease, (2) early corticosteroids treatment causing augmented viral deoxyribonucleic acid/ribonucleic acid (DNA/RNA) replication in pericardial tissue

leading to increased viral antigen exposure, (3) reinfection, and (4) exacerbation of the connective tissue disease. Evidence for an immunopathological process includes (1) the latent period lasting for months; (2) the presence of anti-heart antibodies; and (3) the quick response to steroid treatment and the similarity and coexistence of recurrent pericarditis with other autoimmune conditions (lupus, serum sickness, polyserositis, postpericardiotomy/postmyocardial infarction syndrome, celiac disease, dermatitis herpetiformis, frequent arthralgias, eosinophilia, allergic drug reaction, and history of allergy). Evidence of a potential underlying genetic disorder in recurrent pericarditis is rare familial clustering with autosomal dominant inheritance with incomplete penetrance and sex-linked inheritance (chronic recurrent pericarditis associated with ocular hypertension) suggested in two families. Precordial pain, often with a pleuritic component, is characteristic. Fever, pericardial rub, dyspnoea, elevated erythrocyte sedimentation rate, and electrocardiographic changes may also occur. Massive pericardial effusion, cardiac tamponade, and pericardial constriction are rare.

Symptomatic management relies on exercise restriction and the regimen used in acute pericarditis. Indomethacin should be avoided in elderly patients due to its flow reduction in the coronaries. Colchicine inhibits mitoses in the cell nucleus, binds to tubulin, inhibits various polymorphonuclear functions, and interferes with transcellular movement of collagen. It was effective for recurrent pericarditis when NSAIDs and corticosteroids failed to prevent relapses. During 1,004 months of colchicine treatment, only 13.7% new recurrences occurred. During the 2,333 months of follow-up, 60.7% of the patients remained recurrence-free. The recommended dose is two mg/day for one or two days, followed by one mg/day (level of evidence B, class I). Corticosteroids should be used only in patients with poor general condition or in frequent crises (level of evidence C, class IIa). A common mistake is to use a dose too low to be effective or to taper the dose too rapidly. The recommended regimen is prednisone 1 to 1.5 mg/kg, for at least one month. If patients do not respond adequately, azathioprine (75 to 100 mg/day) or cyclophosphamide can be added. Tapering of corticoids should occur over a three-month period. If symptoms recur during the taper, return to the last dose that suppressed the manifestations, maintain that dose for 2 to 3 weeks, and then recommence tapering. Towards the end of the taper, introduce anti-inflammatory treatment with colchicines or NSAIDs. Renewed treatment should continue for at least three months. Pericardiectomy is indicated only in frequent and highly symptomatic recurrences resistant to medical treatment (level of evidence B, class IIa). Before pericardiectomy, the patient should be on a steroid-free regimen for several weeks. Post pericardiectomy recurrences were also demonstrated, possibly due to incomplete resection of the pericardium.

Pericardial effusion and cardiac tamponade

Pericardial effusion may appear as transudate (hydropericardium), exudate, pyopericardium, or haemopericardium. Large effusions are common with neoplastic, tuberculous, cholesterol, uremic pericarditis, myxedema, and parasitoses. Effusions that develop slowly can be remarkably asymptomatic, while rapidly accumulating smaller effusions can present with tamponade. Loculated effusions are more common when scarring has supervened (e.g., postsurgical, posttrauma, postpurulent pericarditis). Massive chronic pericardial effusions are rare (2 to 3.5% of all large effusions). Cardiac tamponade is the decompensated phase of cardiac compression caused by effusion accumulation and the increased

intrapericardial pressure. In "surgical" tamponade, intrapericardial pressure is rising rapidly, in the matter of minutes to hours (i.e., haemorrhage), whereas a low-intensity inflammatory process is developing in days to weeks before cardiac compression occurs ("medical" tamponade). The volume of fluid causing tamponade varies inversely with both parietal pericardial stiffness and thickness (150 to 2,000 mL). In local compression, dyspnoea, dysphagia, hoarseness (recurrent laryngeal nerve), hiccups (phrenic nerve), or nausea (diaphragm) can occur. Heart sounds are distant. Compression of the base of the lung results in a dullness under the left scapula (Bamberger–Pins–Ewart's sign). In tamponade, chest discomfort, tachypnea, and dyspnoea on exertion progress to orthopnoea, cough, and dysphagia, occasionally also with episodes of unconsciousness. Insidiously developing tamponade may present with the signs of its complications (renal failure, abdominal plethora, shock liver and mesenteric ischaemia). In 60% of the patients, the cause of pericardial effusion may be a known medical condition. Tamponade without two or more inflammatory signs (typical pain, pericardial friction rub, fever, diffuse ST segment elevation) is usually associated with a malignant effusion (likelihood ratio 2.9). Electrocardiography may demonstrate diminished QRS and T-wave voltages, PR-segment depression, ST-T changes, bundle branch block, and electrical alternans (rarely seen in the absence of tamponade). In chest radiography large effusions are depicted as globular cardiomegaly with sharp margins ("water bottle" silhouette). On well-penetrated lateral radiographies, or better on cine films, pericardial fluid is suggested by lucent lines within the cardiopericardial shadow (epicardial halo sign or various other terms for this phenomenon). Recently, it was suggested that this sign might be useful for fluoroscopic guidance of pericardiocentesis. The separation of pericardial layers can be detected in echocardiography, when the pericardial fluid exceeds 15 to 35 mL (Please refer to figure 1 of the original guideline document for information on the Horowitz classification of pericardial effusions). The size of effusions can be graded as (1) small (echo-free space in diastole <10 mm), (2) moderate (at least $\geq$10 mm posteriorly), (3) large ($\geq$20 mm), or (4) very large ($\geq$20 mm and compression of the heart). In large pericardial effusions, the heart may move freely within the pericardial cavity ("swinging heart"). This exaggerated motion of the heart induces "pseudo" motions like pseudomitral valve prolapse, pseudosystolic anterior motion of the mitral valve, paradoxical motion of the interventricular septum, and midsystolic aortic valve closure. Importantly, effusion size is an overall predictor of prognosis: large effusions generally indicate more serious disease. Two-dimensional echocardiography also provides information about the nature of the fluid, suggesting the presence of fibrin, clot, tumour, air, and calcium. Intrapericardial bands, often found after radiation of the chest, are frequently combined with a thick visceral or parietal pericardium. Rarely tumour masses, sometimes cauliflower-like, are found within or adjacent to the pericardium. In parasternal long-axis view, pericardial fluid reflects at the posterior atrioventricular groove, while pleural fluid continues under the left atrium, posterior to the descending aorta. Diagnostic pitfalls are small loculated effusions, haematoma, cysts, tumours, foramen of Morgagni hernia, hiatus hernia, lipodystrophia with paracardial fat, inferior left pulmonary vein, left pleural effusion, mitral annulus calcification, giant left atrium, epicardial fat (best differentiated in CT), and left ventricular pseudoaneurysm. Metastatic infiltration of the pericardium may masquerade pericardial tamponade in echocardiography in patients with no pericardial effusion. After open-heart surgery, localized effusion at the posterior wall can be found with complete compression of the right atrium leading to cardiac tamponade. This may be misinterpreted as atrial myxoma or other cardiac tumour. When bleeding into the pericardium occurs and thrombosis

develops, the typical echolucent areas may disappear, so that development of cardiac tamponade may be overlooked. Transesophageal echocardiography is particularly useful in postoperative loculated pericardial effusion or intrapericardial clot as well as in identifying metastases and pericardial thickening. CT, spin-echo, and cine MRI can also be used to assess the size and extent of simple and complex pericardial effusions. The effusions measured by CT or by MRI may tend to be larger than by echocardiography. Up to one-third of patients with asymptomatic large pericardial chronic effusion developed unexpected cardiac tamponade. Triggers for tamponade include hypovolemia, paroxysmal tachyarrhythmia, and intercurrent acute pericarditis; often no trigger is identifiable. Major diagnostic findings in cardiac tamponade are noted in Table 4 and Focus box 2 of the original guideline document.

Pericardiocentesis may not be necessary when the diagnosis can be made based on other systemic features or the effusions are very small or resolving under anti-inflammatory treatment. Where doubt remains, pericardiocentesis, pericardioscopy, and epicardial and pericardial biopsy (including PCR, immunocytochemistry, and immunohistochemistry) may be valuable (level of evidence B, class IIa). Please see above and refer to focus box 1 of the original guideline document for information on pericardiocentesis. Haemodynamic compromise and cardiac tamponade is an absolute indication for drainage (class I). Patients with dehydration and hypovolemia may temporarily improve with intravenous fluids enhancing ventricular filling. Pericardiocentesis is not applicable in wounds, ruptured ventricular aneurysm, or dissecting aortic haematoma, when clotting makes needle evacuation impossible so that surgical drainage with suppression of bleeding sources is mandatory. Loculated effusions may require thoracoscopic drainage, subxyphoid window, or open surgery. All patients should be monitored for postdrainage decompensation. Whenever possible, treatment should be aimed at the underlying aetiology rather than the effusion itself. However, even in idiopathic effusions extended pericardial catheter drainage (3 $\pm$ 2 days, range 1 to 13 days) was associated with a trend to lower recurrence rates (6% vs. 23%) than in those without catheter drainage during the follow-up of 3.8 $\pm$ 4.3 years. Resistant neoplastic processes require intrapericardial treatment, percutaneous balloon pericardiotomy, or rarely pericardiectomy. Surgical approach is recommended only in patients with very large chronic effusion (with or without symptoms) in whom repeated pericardiocentesis and/or intrapericardial therapy were not successful.

Constrictive pericarditis

Constrictive pericarditis is a rare but severely disabling consequence of the chronic inflammation of the pericardium, leading to an impaired filling of the ventricles and reduced ventricular function. Tuberculosis, mediastinal irradiation, and previous cardiac surgical procedures are frequent causes of the disease, which can present in several pathoanatomical forms (please refer to figure 2 of the original guideline document for information on the pathoanatomical forms of constrictive pericarditis vs. restrictive cardiomyopathy). Constrictive pericarditis may rarely develop only in the epicardial layer in patients with previously removed parietal pericardium. Transient constrictive pericarditis is rare entity, distinguished by its self-limiting nature. Patients complain about fatigue, peripheral oedema, breathlessness, and abdominal swelling, which may be aggravated by a protein-loosing enteropathy. Typically, there is a long delay

between the initial pericardial inflammation and the onset of constriction. In decompensated patients, 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. Clinical, echocardiographic, and haemodynamic parameters can be derived from Table 5 of the original guideline document. Differential diagnosis has to include acute dilatation of the heart, pulmonary embolism, right ventricular infarction, pleural effusion, chronic obstructive lung diseases, and restrictive cardiomyopathy. The best way to distinguish constrictive pericarditis from restrictive cardiomyopathy is the analysis of respiratory changes with or without changes of preload by Doppler and/or tissue Doppler echocardiography, but physical findings, ECG, chest radiography, CT and MRI, haemodynamics, and endomyocardial biopsy may be helpful as well (Please refer to table 6 of the original guideline document for information on differential diagnosis: constrictive pericarditis vs. restrictive cardiomyopathy).

Pericardiectomy is the only treatment for permanent constriction. The indications are based upon clinical symptoms, echocardiography findings, CT/MRI, and heart catheterisation. There are two standard approaches, both aiming at resecting the diseased pericardium as far as possible: (1) the antero-lateral thoracotomy (fifth intercostal space) and (2) median sternotomy (faster access to the aorta and right atrium for extracorporeal circulation). A primary installation of cardiopulmonary bypass is not recommended, due to the enhanced diffuse bleeding during dissection of the pericardium, following systemic heparinisation. If severe calcified adhesions between peri- and epicardium or a general affection of the epicardium ("outer porcelain heart") are present, surgery carries a high risk of either incomplete success or severe myocardial damage. An alternative approach in such cases may be a "laser shaving" using an Excimer laser. Areas of strong calcification or dense scarring may be left as islands to avoid major bleeding. Pericardiectomy for constrictive pericarditis has a mortality rate of 6 to 12% in the current series. The complete normalization of cardiac haemodynamics is reported in only 60% of the patients. The deceleration time (DT) may remain prolonged, and postoperative respiratory variations of mitral/tricuspid flow are found in 9 to 25%. Left ventricular ejection fraction increases due to a better ventricular filling, but consistent changes of the left and right atrial sizes were not reported. Major complications include acute perioperative cardiac insufficiency and ventricular wall rupture. Cardiac mortality and morbidity at pericardiectomy is mainly caused by the presurgically unrecognised presence of myocardial atrophy or myocardial fibrosis (Please refer to figure 2 of the original guideline document for information on the pathoanatomical forms of constrictive pericarditis vs. restrictive cardiomyopathy). Myocardial atrophy in CT is characterized by (1) thinning of the interventricular septum and posterolateral wall (<1 cm), (2) reduction of the wall thickening during the cardiac cycle (<40%), and (3) reduction of the left-ventricular muscle mass (LVMM)/end-diastolic volume (EDV) ratio (<1). Myocardial fibrosis should be considered whenever the thickened/calcified pericardium is not separated from the myocardium by subepicardial fat and when the myocardial wall is showing wave-like appearance with wall thinning. Exclusion of patients with extensive myocardial fibrosis and/or atrophy led to a reduction of the mortality rate for pericardiectomy to 5%. Postoperative low cardiac output should be treated by fluid substitution and catecholamines, high doses of digitalis, and intra-aortic balloon pump in most severe cases. If indication for surgery was established early, long-term survival after pericardiectomy corresponds to that of the general population. However, if severe clinical symptoms were present for a

longer period before surgery, even a complete pericardiectomy may not achieve a total restitution.

Pericardial cysts

Congenital pericardial cysts are uncommon and may have both unilocular and multilocular forms, with the diameter from 1 to 5 cm. Inflammatory cysts comprise pseudocysts as well as encapsulated and loculated pericardial effusions, caused by rheumatic pericarditis, bacterial infection, particularly tuberculosis, trauma, and cardiac surgery. Echinococcal cysts usually originate from ruptured hydatid cysts in the liver and lungs. Most patients are asymptomatic and cysts are detected incidentally on chest roentgenograms as an oval, homogeneous radiodense lesion, usually at the right cardiophrenic angle. However, the patients can also present with chest discomfort, dyspnoea, cough, or palpitations, due to the compression of the heart. Echocardiography is useful, but additional imaging by CT (density readings) or MRI is often needed.

The treatment for congenital and inflammatory cysts is percutaneous aspiration and ethanol sclerosis. If this is not feasible, video assisted thoracotomy or surgical resection may be necessary. The surgical excision of echinococcal cysts is not recommended. Percutaneous aspiration and instillation of ethanol or silver nitrate after pretreatment with Albendazole (800 mg/day 4 weeks) is safe and effective.

Specific forms of pericarditis

Viral pericarditis

Viral pericarditis is the most common infection of the pericardium. Inflammatory abnormalities are due to direct viral attack, the immune response (antiviral or anticardiac), or both. Early viral replication in pericardial and epimyocardial tissue elicits cellular and humoral immune responses against the virus and/or cardiac tissue. Viral genomic fragments in pericardial tissue may not necessarily replicate, yet they serve as a source of antigen to stimulate immune responses. Deposits of immunoglobulin M (IgM), immunoglobulin G (IgG), and occasionally immunoglobulin A (IgA), can be found in the pericardium and myocardium for years. Various viruses cause pericarditis (entero-, echo-, adeno-, cytomegalo-, Ebstein Barr-, herpes simplex-, influenza, parvo B19, hepatitis C, human immunodeficiency virus (HIV), etc.). Attacks of enteroviral pericarditis follow the seasonal epidemics of Coxsackie virus A+B and Echovirus infections. Cytomegalovirus pericarditis has an increased incidence in immunocompromised and HIV infected hosts. Infectious mononucleosis with sore throat, adenopathy, and positive mumps or Epstein Barr virus (EBV) serology may also present with pericarditis.

The diagnosis of viral pericarditis is not possible without the evaluation of pericardial effusion and/or pericardial/epicardial tissue, preferably by PCR or in-situ hybridisation (level of evidence B, class IIa) (please refer to focus boxes 3 to 5 of the original guideline document for information on analyses of pericardial effusion, pericardioscopy and epicardial/pericardial biopsy, and epicardial/pericardial tissue analyses). A fourfold rise in serum antibody levels is suggestive but not diagnostic for viral pericarditis (level of evidence B, class IIb).

Treatment of viral pericarditis is directed to resolve symptoms (see acute pericarditis), prevent complications, and eradicate the virus. In patients with chronic or recurrent symptomatic pericardial effusion and confirmed viral infection, the following specific treatment is under investigation: (1) cytomegalovirus (CMV) pericarditis: hyperimmunoglobulin – 1 time per day 4 mL/kg on day 0, 4, and 8; 2 mL/kg on day 12 and 16; (2) Coxsackie B pericarditis: Interferon alpha: 2.5 Mio. IU/m^2 surface area subcutaneously 3x per week; (3) adenovirus and parvovirus B19 perimyocarditis: immunoglobulin treatment: 10 g intravenously at day 1 and 3 for 6 to 8 h.

Pericardial manifestation of HIV infection can be due to infective, noninfective, and neoplastic diseases (Kaposi sarcoma and/or lymphoma). Infective (myo)pericarditis results from the local HIV infection and/or from the other viral (cytomegalovirus, herpes simplex), bacterial (*Staphylococcus aureus*, *Klebsiella pneumoniae*, *Mycobacterium avium*, and tuberculosis) and fungal coinfections (Cryptococcus neoformans). In progressive disease the incidence of echocardiographically detected pericardial effusion is up to 40%. Cardiac tamponade is rare. During the treatment with retroviral compounds, lipodystrophy can develop (best demonstrated by MRI) with intense paracardial fat deposition leading to heart failure. Treatment is symptomatic, while in large effusions and cardiac tamponade pericardiocentesis is necessary. The use of corticoid therapy is contraindicated except in patients with secondary tuberculous pericarditis, as an adjunct to tuberculostatic treatment (level of evidence A, class I).

Bacterial pericarditis

Purulent pericarditis in adults is rare (please refer to table 7 of the original guideline document for information on the differential diagnosis of the specific forms of pericarditis) but always fatal if untreated. Mortality rate in treated patients is 40%, mostly due to cardiac tamponade, toxicity, and constriction. It is usually a complication of an infection originating elsewhere in the body, arising by contiguous spread or haematogenous dissemination. Predisposing conditions are preexisting pericardial effusion, immunosuppression, chronic diseases (alcohol abuse, rheumatoid arthritis, etc), cardiac surgery, and chest trauma. Rarely, left ventricular pseudoaneurysm may complicate bacterial pericarditis.

The disease appears as an acute, fulminant infectious illness with short duration. Percutaneous pericardiocentesis must be promptly performed. Obtained pericardial fluid should undergo urgent Gram, acid-fast, and fungal staining, followed by cultures of the pericardial and body fluids (level of evidence B, class I).

Rinsing of the pericardial cavity, combined with effective systemic antibiotic therapy, is mandatory (combination of antistaphylococcal antibiotic and aminoglycoside, followed by tailored antibiotic therapy according to the results of pericardial fluid and blood cultures). Intrapericardial instillation of antibiotics (e.g., gentamycin) is useful but not sufficient. Frequent irrigation of the pericardial cavity with urokinase or streptokinase using large catheters may liquefy the purulent exudate, but open surgical drainage through subxiphoid pericardiotomy is preferable. Pericardiectomy is required in patients with dense adhesions, loculated and thick purulent effusion, recurrence of tamponade, persistent infection, and progression to constriction. Surgical mortality up to 8% was

reported for pericardiectomy combined with antibiotic treatment, but the total mortality is higher.

Tuberculous (TBC) pericarditis

In the last decade TBC pericarditis in the developed countries has been primarily seen in immunocompromised patients (acquired immunodeficiency syndrome [AIDS]). The mortality rate in untreated acute effusive TBC pericarditis approaches 85%. Pericardial constriction occurs in 30 to 50%. The clinical presentation is variable: acute pericarditis with or without effusion; cardiac tamponade; silent, often large, pericardial effusion with a relapsing course; toxic symptoms with persistent fever; acute constrictive pericarditis; subacute constriction; effusive-constrictive or chronic constrictive pericarditis; and pericardial calcifications. The diagnosis is made by the identification of *Mycobacterium tuberculosis* in the pericardial fluid or tissue and/or the presence of caseous granulomas in the pericardium. Pericarditis in a patient with proven extracardiac tuberculosis is strongly suggestive of TBC aetiology (several sputum cultures should be taken). The tuberculin skin test may be false negative in 25 to 33% of patients and false positive in 30 to 40% (elderly patients). A more accurate enzyme-linked immunospot (ELISPOT) test was recently developed, detecting T-cells specific for *Mycobacterium tuberculosis* antigen. Perimyocardial TBC involvement is also associated with high titres of antimyolemmal and antimyosin antibodies in the sera. The diagnostic yield of pericardiocentesis in TBC pericarditis ranges from 30 to 76% according to the methods applied for the analyses of pericardial effusion. Pericardial fluid demonstrates high specific gravity, high protein levels, and high white-cell count (from 0.7 to 54 x 10^9/L). Importantly, PCR can identify DNA of *Mycobacterium tuberculosis* rapidly from only 1 microliter of pericardial fluid. High adenosine deaminase activity and interferon gamma concentration in pericardial effusion are also diagnostic, with a high sensitivity and specificity (please refer to Focus box 4 of the original guideline document for information on pericardioscopy and epicardial/pericardial biopsy): Both pericardioscopy and pericardial biopsy have also improved the diagnostic accuracy for TBC pericarditis. Pericardial biopsy enables rapid diagnosis with better sensitivity than pericardiocentesis (100 vs. 33%).

Various antituberculous drug combinations of different lengths (6, 9, 12 months) have been applied. However, only patients with proven or very likely TBC pericarditis should be treated. Prevention of constriction in chronic pericardial effusion of undetermined aetiology by "ex iuvantibus" antitubercular treatment was not successful. The use of steroids remains controversial. A meta- analysis of patients with effusive and constrictive TBC pericarditis suggested that tuberculostatic treatment combined with steroids might be associated with fewer deaths, less frequent need for pericardiocentesis or pericardiectomy (level of evidence A, class IIa). If given, prednisone should be administered in relatively high doses (1 to 2 mg/kg per day) since rifampicin induces its liver metabolism. This dose is maintained for 5 to 7 days and is progressively reduced to discontinuation in 6 to 8 weeks. If, in spite of combination therapy, constriction develops pericardiectomy is indicated (level of evidence B, class I).

Pericarditis in renal failure

Renal failure is a common cause of pericardial disease, producing large pericardial effusions in up to 20% of patients. Two forms have been described: (1) Uremic pericarditis – in 6 to 10% of patients with advanced renal failure (acute or chronic) before dialysis has been instituted or shortly thereafter. It results from inflammation of the visceral and parietal pericardium and correlates with the degree of azotemia (the blood urea nitrogen [BUN] is usually >60 mg/dL). (2) Dialysis-associated pericarditis – in up to 13% of patients on maintenance haemodialysis, and occasionally with chronic peritoneal dialysis due to inadequate dialysis and/or fluid overload. Pathologic examination of the pericardium shows adhesions between the thickened pericardial membranes ("bread and butter" appearance). The clinical features may include fever and pleuritic chest pain, but many patients are asymptomatic. Pericardial rubs may persist even in large effusions or may be transient. Due to autonomic impairment in uremic patients, heart rate may remain slow (60 to 80 beats/min) during tamponade, despite fever and hypotension. Anaemia, due to induced resistance to erythropoetin may worsen the clinical picture. The ECG does not show the typical diffuse ST/T wave elevations observed with other causes of acute pericarditis due to the lack of the myocardial inflammation. If the ECG is typical of acute pericarditis, intercurrent infection must be suspected.

Most patients with uremic pericarditis respond rapidly to haemo- or peritoneal dialysis with resolution of chest pain and pericardial effusion. To avoid haemopericardium, heparin-free haemodialysis should be used. Care should be taken since acute fluid removal with haemodialysis can lead to cardiovascular collapse in patients with tamponade or pre-tamponade. Hypokalemia and hypophosphatemia should be prevented by supplementing the dialysis solution when appropriate. Intensified dialysis usually leads to resolution of the pericarditis within 1 to 2 weeks. Peritoneal dialysis, which does not require heparinisation, may be therapeutic in pericarditis resistant to haemodialysis, or if heparin-free haemodialysis cannot be performed. NSAIDs and systemic corticosteroids have limited success when intensive dialysis is ineffective. Cardiac tamponade and large chronic effusions resistant to dialysis must be treated with pericardiocentesis (level of evidence B, class IIa). Large, non-resolving symptomatic effusions should be treated with instillation of intrapericardial corticosteroids after pericardiocentesis or subxiphoid pericardiotomy (triamcinolone hexacetonide 50 mg every 6 h for 2 to 3 days). Pericardiectomy is indicated only in refractory, severely symptomatic patients due to its potential morbidity and mortality. Within two months after renal transplantation pericarditis has been reported in 2.4% of patients. Uraemia or infection (CMV) may be the causes.

Autoreactive pericarditis and pericardial involvement in systemic autoimmune diseases

The diagnosis of autoreactive pericarditis is established using the following criteria: (1) increased number of lymphocytes and mononuclear cells >5,000/mm^3 (autoreactive lymphocytic), or the presence of antibodies against heart muscle tissue (antisarcolemmal) in the pericardial fluid (autoreactive antibody-mediated); (2) signs of myocarditis on epicardial/endomyocardial biopsies by $\geq$14 cells/mm^2; (3) exclusion of active viral infection both in pericardial effusion and endomyocardial/epimyocardial biopsies (no virus isolation, no IgM-titer against cardiotropic viruses in pericardial effusion, and negative PCR for major cardiotropic viruses); (4) tuberculosis, *Borrelia burgdorferi*, *Chlamydia*

pneumoniae, and other bacterial infection excluded by PCR and/or cultures; (5) neoplastic infiltration absent in pericardial effusion and biopsy samples; (6) exclusion of systemic, metabolic disorders, and uraemia. Intrapericardial treatment with triamcinolone is highly efficient with low incidence of side effects.

Pericarditis, with or without effusion, is also a component of a multiserositis in systemic autoimmune diseases: rheumatoid arthritis, systemic lupus erythematosus (SLE), progressive systemic sclerosis, polymyositis/ dermatomyositis, mixed connective tissue disease, seronegative spondyloarthropathies, systemic and hypersensitivity vasculitides, Behcet syndrome, Wegener granulomatosis, and sarcoidosis. Intensified treatment of the underlying disease and symptomatic management are indicated (level of evidence B, class I). Treatment should focus on pericardial symptoms, management of the pericardial effusion, and the underlying systemic disease.

The post-cardiac injury syndrome: postpericardiotomy syndrome

Post-cardiac injury syndrome develops within days to months after cardiac, pericardial injury or both. It resembles the post-myocardial infarction syndrome, both appearing to be variants of a common immunopathic process. Unlike post-myocardial infarction syndrome, post-cardiac injury syndrome acutely provokes a greater antiheart antibody response (antisarcolemmal and antifibrillary), probably related to more extensive release of antigenic material. Pericardial effusion also occurs after orthotopic heart transplantation (21%). It is more frequent in patients receiving aminocaproic acid during the operation. Cardiac tamponade after open heart surgery is more common following valve surgery (73%) than coronary artery bypass grafting (CABG) alone (24%) and may be related to the preoperative use of anticoagulants. Constrictive pericarditis may also occur after cardiac surgery. Warfarin administration in patients with early postoperative pericardial effusion imposes the greatest risk, particularly in those who did not undergo pericardiocentesis and drainage of the effusion. Symptomatic treatment is as in acute pericarditis (NSAIDs or colchicine for several weeks or months, even after disappearance of effusion). Long-term (3 to 6 months) oral corticoids or preferably pericardiocentesis and intrapericardial instillation of triamcinolone (300 mg/m^2) are therapeutic options in refractory forms. Redo surgery and pericardiectomy are very rarely needed. Primary prevention of postpericardiotomy syndrome using short-term perioperative steroid treatment or colchicine is under investigation.

Postinfarction pericarditis

Two forms of postinfarction pericarditis can be distinguished: an "early" form (pericarditis epistenocardica) and a "delayed" form (Dressler's syndrome). Epistenocardiac pericarditis, caused by direct exudation, occurs in 5 to 20% of transmural myocardial infarctions but is clinically discovered rarely. Dressler's syndrome occurs from one week to several months after clinical onset of myocardial infarction, with symptoms and manifestations similar to the post-cardiac injury syndrome. It does not require transmural infarction and can also appear as an extension of epistenocardiac pericarditis. Its incidence is 0.5 to 5% and is still lower in patients treated with thrombolytics (<0.5%), but was more frequent in cases of pericardial bleeding after antithrombotic treatment. Of note, ECG changes are often overshadowed by myocardial infarction changes. Stage I

ECG changes are uncommon and suggest "early" post-myocardial infarction syndrome whereas failure to evolve or "resurrection" of previously inverted T waves strongly suggest myocardial infarction pericarditis. Postinfarction pericardial effusion >10 mm is most frequently associated with haemopericardium, and two thirds of these patients may develop tamponade/free wall rupture. Urgent surgical treatment is life saving. However, if the immediate surgery is not available or contraindicated pericardiocentesis and intrapericardial fibrin-glue instillation could be an alternative in subacute tamponade.

Hospitalisation to observe for tamponade, differential diagnosis, and adjustments of treatment is needed. Ibuprofen, which increases coronary flow, is the agent of choice. Aspirin, up to 650 mg every 4 h for 2 to 5 days has also been successfully applied. Other nonsteroidal agents risk thinning the infarction zone. Corticosteroid therapy can be used for refractory symptoms only but could delay myocardial infarction healing (level of evidence B, class IIa).

Traumatic pericardial effusion and haemopericardium in aortic dissection

Direct pericardial injury can be induced by accidents or iatrogenic wounds. Blood loss, vasoconstriction, and haematothorax leading to severe hypotension and shock may mask pulses paradoxus. Thoracotomy and surgical repair should be performed to stabilize the haemodynamics.

Iatrogenic tamponade occurs most frequently in percutaneous mitral valvuloplasty, during or after transseptal puncture, particularly if no biplane catheterisation laboratory is available and a small left atrium is present. Whereas the puncture of the interatrial septum is asymptomatic, the passage of the free wall induces chest-pain immediately. If high-pressure containing structures are punctured, rapid deterioration occurs. However, if only the atrial wall is passed, the onset of symptoms and the tamponade may be delayed for 4 to 6 h. Rescue pericardiocentesis is successful in 95 to 100% with a mortality of less than 1% (please refer to table 8 of the original guideline document for information on traumatic pericardial effusion).

Dissection of the coronary artery and acute or subacute cardiac tamponade may occur during percutaneous coronary interventions. A breakthrough in the treatment of coronary perforation is membrane-covered graft stents. Perforation of the coronary artery by a guidewire is not infrequent and causes very rarely a relevant pericardial haemorrhage.

During right ventricular endomyocardial biopsy due to the low stiffness of the myocardium, the catheter may pass the myocardium, particularly, when the bioptome has not been opened before reaching the endocardial border. The rate of perforation is reported to be in the range of 0.3 to 5%, leading to tamponade and circulatory collapse in less than half of the cases. The incidence of pericardial haemorrhage in left ventricular endomyocardial biopsy is lower (0.1 to 3.3%). Frank cardiac perforations seem to be accompanied by sudden bradycardia and hypotension. Severe complications, leading to procedure related mortality were reported in only 0.05% in a worldwide survey of more than 6,000 cases and in none of the 2,537 patients from the registry of an experienced reference centre.

Pacemaker leads penetrating the right ventricle or epicardial fixed electrodes may cause pericarditis with tamponade, adhesions, or constriction. A right bundle brand block instead of a usually induced left bundle branch block can be a first clue.

Blunt chest trauma is the major risk of car accidents. The deceleration force can lead to myocardial contusion with intrapericardial haemorrhage, cardiac rupture, pericardial rupture, or herniation. Transesophageal echocardiography in the emergency room or immediate CT should be performed. Indirect injury of the pericardium is more difficult to detect. Pericardial laceration and partial extrusion of the heart into the mediastinum and pleural space may also occur after injury.

In dissection of the ascending aorta, pericardial effusion can be found in 17 to 45% of the patients and in 48% of the autopsy cases (Please refer to table 8 of the original guideline document for information on traumatic pericardial effusion). In a clinical series of aortic dissection, pericardial tamponade was found by CT, MRI, or echocardiography in 17 to 33% of patients with type I dissection and 18 to 45% in type II dissection and 6% in type III dissection. Pericardiocentesis is contraindicated, due to the risk of intensified bleeding and extension of the dissection. Surgery should be performed immediately after the diagnosis is established by echocardiography and/or CT/MRI, even if no coronary angiography or aortography is available (level of evidence B, class I).

Neoplastic pericarditis

Primary tumours of the pericardium are 40 times less common than the metastatic ones. Mesothelioma, the most common of the primary tumours, is almost always incurable. Metastatic tumours of the pericardium are found in 15 to 30% of all autopsies performed in patients with malignant disease and in 4% in general autopsies. The most common secondary malignant tumours are lung cancer, breast cancer, malignant melanoma, lymphomas, and leukemias. Effusions may be small or large with an imminent tamponade (frequent recurrences) or constriction. It even may be the initial sign of malignant disease. The majority of patients with malignant pericardial effusion are asymptomatic, particularly if the accumulation of pericardial effusion is gradual. The onset of dyspnoea, cough, chest pain, tachycardia, and jugular venous distension is observed when the volume of fluid exceeds 500 mL. Orthopnea, weakness, dysphagia, syncope, palpitations, pericardial friction rub, hiccups, distant heart sounds, pleural effusion, hepatomegaly, oliguria, and oedema can also be present. Pulsus paradoxus, hypotension, cardiogenic shock, and paradoxical movement of the jugular venous pulse are important signs of cardiac tamponade.

The diagnosis is based on the confirmation of the malignant infiltration within pericardial sac. Of note, in almost two thirds of the patients with documented malignancy, pericardial effusion is caused by non-malignant diseases (e.g., radiation pericarditis) or opportunistic infections. The chest roentgenogram, CT, and MRI may reveal mediastinal widening, hilar masses, and pleural effusion. The analyses of pericardial fluid and pericardial or epicardial biopsy are essential for the confirmation of malignant pericardial disease (level of evidence B, class I) (please refer to Focus boxes 3 to 5 of the original guideline document for information on analyses of pericardial effusion, pericardioscopy and epicardial/pericardial biopsy, and epicardial/pericardial tissue analyses).

Treatment of cardiac tamponade is a class I indication for pericardiocentesis. The following steps are recommended in suspected neoplastic pericardial effusion without tamponade: (1) systemic antineoplastic treatment as baseline therapy which can prevent recurrences in up to 67% of cases (level of evidence B, class I); (2) pericardiocentesis to relieve symptoms and establish diagnosis (level of evidence B, class IIa); (3) intrapericardial instillation of cytostatic/sclerosing agent (level of evidence B, class IIa). Pericardial drainage is recommended, when technically possible, in all patients with large effusions because of the high recurrence rate (40 to 70%) (level of evidence B, class I). Prevention of recurrences, may be achieved by intrapericardial instillation of: sclerosing, cytotoxic agents, or immunomodulators. Intrapericardial treatment tailored to the type of the tumour indicate that administration of cisplatin is most effective in secondary lung cancer and intrapericardial instillation of thiotepa was more effective in breast cancer pericardial metastases. No patient showed signs of constrictive pericarditis (for both agents, level of evidence B, class IIa). Tetracycline as sclerosing agents also control the malignant pericardial effusion in around 85% of cases, but side effects and complications are quite frequent: fever (19%), chest pain (20%), and atrial arrhythmias (10%) (level of evidence B, class IIb). Although classic sclerotherapy after intrapericardial instillation of tetracycline, doxycycline, minocycline and bleomycin is an effective procedure, constrictive pericarditis secondary to fibrosis remains a severe problem in long-term survivors. Although intrapericardial administration of radionuclides has yielded very good results, it is not widely accepted because of the logistic problems connected with their radioactivity (level of evidence B, class IIa). Radiation therapy is very effective (93%) in controlling malignant pericardial effusion (level of evidence B, class IIa) in patients with radiosensitive tumours such as lymphomas and leukemias. However, radiotherapy of the heart can cause myocarditis and pericarditis by itself. Subxyphoid pericardiotomy is indicated when pericardiocentesis cannot be performed (level of evidence B, class IIb). The procedure can be carried out in local anaesthesia, but complications include myocardial laceration, pneumothorax, and mortality. Pleuropericardiotomy allows drainage of malignant pericardial fluid into the pleural space (level of evidence C, class IIb). It is associated with a higher complications rate and offers no advantage over pericardiocentesis or subxyphoid pericardiotomy. Pericardiectomy is rarely indicated, mainly for pericardial constriction or complications of previous procedures.

Percutaneous balloon pericardiotomy creates a pleuro-pericardial direct communication, which allows fluid drainage into the pleural space (level of evidence B, class IIa). In large malignant pericardial effusions and recurrent tamponade, it seems to be effective (90 to 97%) and safe but has the potential risk of dissemination of neoplastic cells.

Rare forms of pericardial disease

Fungal pericarditis

Fungal pericarditis occurs mainly in immunocompromised patients or in the course of endemic-acquired fungal infections. The clinical picture comprises the full spectrum of pericardial diseases, including fungal myocarditis. Fungal pericarditis is mainly due to endemic fungi (Histoplasma, Coccidioides), or nonendemic opportunistic fungi (Candida, Aspergillus, Blastomyces) and semifungi (Nocardia,

Actinomyces). Diagnosis is obtained by staining and culturing pericardial fluid or tissue. Antifungal antibodies in serum are also helpful in establishing the diagnosis of fungal infection. Antifungal treatment with fluconazole, ketoconasole, itraconasole, amphotericin B, liposomal amphotericin B, or amphotericin B lipid complex is indicated in patients with documented fungal pericarditis (level of evidence B, class I). Corticosteroids and NSAIDs can support the treatment with antifungal drugs (level of evidence C, class IIa). Patients with pericarditis in the course of histoplasmosis do not need antifungal therapy, but respond to NSAIDs given during 2 to 12 weeks. Sulfonamides are the drugs of choice for a nocardiosis infection. Combination of three antibiotics including penicillin should be given for actinomycosis (level of evidence C, class I). Pericardiocentesis or surgical treatment is indicated for haemodynamic impairment. Pericardiectomy is indicated in fungal constrictive pericarditis (level of evidence C, class I).

Radiation pericarditis

The probability to develop radiation-induced pericarditis is influenced by the applied source, dose, its fractionation, duration, radiation exposed volume, form of mantel field therapy, and the age of the patients. Radiation-induced pericarditis may occur already during the therapy or months and years later – with latency of up to 15 to 20 years. The effusion may be serous or haemorrhagic, later on with fibrinous adhesions or constriction, typically without tissue calcification. The symptoms may be masked by the underlying disease or the applied chemotherapy. Imaging should start with echocardiography, followed by cardiac CT or MRI if necessary. Pericarditis without tamponade may be treated conservatively or by pericardiocentesis for diagnostic purposes or if haemodynamic compromise/tamponade occurs. Pericardial constriction may happen in up to 20% of patients, requiring pericardiectomy. The operative mortality is high (21%) and the postoperative five years survival rate is very low (1%) mostly due to myocardial fibrosis.

Chylopericardium

Chylopericardium refers to a communication between the pericardial sac and the thoracic duct, as a result of trauma, congenital anomalies, or as a complication of open-heart surgery, mediastinal lymphangiomas, lymphangiomatous hamartomas, lymphangiectasis, and obstruction or anomalies of the thoracic duct. Infection, tamponade, or constriction may aggravate the prognosis. The pericardial fluid is sterile, odourless, and opalescent with a milky white appearance and the microscopic finding of fat droplets. The chylous nature of the fluid is confirmed by its alkaline reaction, specific gravity between 1010 and 1021, Sudan III stain for fat, the high concentrations of triglycerides (5 to 50 g/L) and protein (22 to 60 g/L). Enhanced CT, alone or combined with lymphography, can identify not only the location of the thoracic duct but also its lymphatic connection to the pericardium. Treatment depends on the aetiology and the amount of chylous accumulation. Chylopericardium after thoracic or cardiac operation without signs of tamponade is preferably treated by pericardiocentesis and diet (medium chain triglycerides). If further production of chylous effusion continues, surgical treatment is mandatory (level of evidence B, class I). When conservative treatment and pericardiocentesis fail, pericardio-peritoneal shunting by a pericardial window is a reasonable option. Alternatively, when the course of the thoracic duct was precisely identified, its ligation and resection just above the

diaphragm is the most effective treatment. In secondary chylopericardium the underlying disease (e.g., mediastinal tumour) should be treated.

Drug- and toxin-related pericarditis

Pericardial reactions to drugs are rare. However, several medications and toxic substances can induce pericarditis, tamponade, adhesions, fibrosis, or constriction (Please refer to table 9 of the original guideline document for information on drug- and toxin-related pericardial diseases). Mechanisms include drug induced lupus reactions, idiosyncrasy, "serum sickness," foreign substance reactions, and immunopathy. Management is based on discontinuation of the causative agent and symptomatic treatment.

Pericardial effusion in thyroid disorders

Pericardial effusion occurs in 5 to 30% of patients with hypothyroidism. Fluid accumulates slowly and tamponade occurs rarely. In some cases cholesterol pericarditis may be observed. The diagnosis of hypothyroidism is based on serum levels of thyroxin and thyroid stimulating hormone. Bradycardia, low-voltage of the QRS and T-wave inversion or flattening in the ECG, cardiomegaly in the roentgenogram, and pericardial effusion in echocardiography, as well as a history of radiation-induced thyroid dysfunction, myopathy, ascites, pleural effusion, and uveal oedema may be observed. Therapy with thyroid hormone decreases pericardial effusion (level of evidence B, class I).

Pericardial effusion in pregnancy

There is no evidence that pregnancy affects susceptibility to pericardial disease. However, many pregnant women develop a minimal to moderate clinically silent hydropericardium by the third trimester. Cardiac compression is rare. ECG changes of acute pericarditis in pregnancy should be distinguished from the slight ST-segment depressions and T-wave changes seen in normal pregnancy (please refer to Table 10 of the original guideline document for information on the diagnostic approach to pericardial effusion in pregnancy). Occult constriction becomes manifest in pregnancy due to the increased blood volume. Most pericardial disorders are managed as in nonpregnant. Caution is necessary while high-dose aspirin may prematurely close the ductus arteriosus, and colchicine is contraindicated in pregnancy. Pericardiotomy and pericardiectomy can be safely performed if necessary and do not impose a risk for subsequent pregnancies. Foetal pericardial fluid can be detected by echocardiography after 20 weeks´ gestation and is normally 2 mm or less in depth. More fluid should raise questions of hydrops foetalis, Rh disease, hypoalbuminemia, and immunopathy or maternally transmitted mycoplasmal or other infections, and neoplasia.

Definitions

Class of Recommendations

Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment

- **Class IIa**: Weight of evidence/opinion is in favour of usefulness/efficacy.
- **Class IIb**: Usefulness/efficacy is less well established by evidence/opinion.

Class III: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful

Level of Evidence

A: Multiple randomised clinical trials or meta-analyses

B: A single randomised trial or nonrandomised studies

C: Consensus opinion of the experts

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate diagnosis and management of pericardial diseases

POTENTIAL HARMS

- Indomethacin should be avoided in elderly patients due to its flow reduction in coronaries.
- The most serious complications of pericardiocentesis are laceration and perforation of the myocardium and the coronary vessels. In addition, patients can experience air embolism, pneumothorax, arrhythmias (usually vasovagal bradycardia), and puncture of the peritoneal cavity or abdominal viscera.
- If severe calcified adhesions between peri- and epicardium or a general affection of the epicardium ("outer porcelain heart") are present, surgery carries a high risk of either incomplete success or severe myocardial damage.

- Tetracycline as sclerosing agents also control the malignant pericardial effusion in around 85% of cases, but side effects and complications are quite frequent: fever (19%), chest pain (20%), and atrial arrhythmias (10%).
- Radiation therapy is very effective (93%) in controlling malignant pericardial effusion in patients with radiosensitive tumours such as lymphomas and leukemias. However, radiotherapy of the heart can cause myocarditis and pericarditis by itself.
- Subxyphoid pericardiotomy is indicated when pericardiocentesis cannot be performed. The procedure can be carried out in local anaesthesia, but complications include myocardial laceration, pneumothorax, and mortality.
- Occult constriction becomes manifest in pregnancy due to the increased blood volume. Most pericardial disorders are managed as in nonpregnant. Caution is necessary while high-dose aspirin may prematurely close the ductus arteriosus.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Pericardiocentesis is life saving in cardiac tamponade. Aortic dissection is a major contraindication. Relative contraindications include uncorrected coagulopathy, anticoagulant therapy, thrombocytopenia <50,000/mm^3, small, posterior, and loculated effusions.
- Pericardiectomy is contraindicated for myocardial atrophy and global form of pericardial constriction with bilateral thickening of the pericardium along both ventricles separated from the right myocardial wall by a thin layer of subepicardial fat (tube-like configuration of both ventricles and enlargement of both atria with thinning of the interventricular septum and posterolareral wall of the left ventricle below 1 cm suggests myocardial atrophy).
- Pericardiectomy is contraindicated for perimyocardial fibrosis and global form of pericardial constriction with bilateral thickening of the pericardium along both ventricles (the right sided thickened pericardium cannot be separated from the wave-like thin form of right sided ventricular wall suggesting perimyocardial fibrosis).
- Pericardial manifestation of human immunodeficiency virus (HIV) infection can be due to infective, non-infective, and neoplastic diseases (Kaposi sarcoma and/or lymphoma). The use of corticoid therapy is contraindicated except in patients with secondary tuberculous pericarditis, as an adjunct to tuberculostatic treatment.
- In a clinical series of aortic dissection, pericardial tamponade was found by computed tomography (CT), magnetic resonance imaging (MRI), or echocardiography in 17 to 33% of patients with type I dissection and 18 to 45% in type II dissection and 6% in type III dissection. Pericardiocentesis is contraindicated, due to the risk of intensified bleeding and extension of the dissection.
- Colchicine is contraindicated in pregnancy.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads
Pocket Guide/Reference Cards
Slide Presentation

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Maisch B, Seferovic PM, Ristic AD, Erbel R, Rienmuller R, Adler Y, Tomkowski WZ, Thiene G, Yacoub MH. Guidelines on the diagnosis and management of pericardial diseases. Sophia Antipolis (FR): European Society of Cardiology; 2004. 28 p. [275 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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GUIDELINE DEVELOPER(S)

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ESC Committee for Practice Guidelines

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The Task Force makes every effort to avoid any actual or potential conflicts of interest that might arise as a result of an outside relationship or personal interest of a member of the writing panel. Specifically, all members of the writing panel, before final approval by the Committee for Practice Guidelines (CPG), are asked to provide disclosure statements of all such relationships that might be perceived as real or potential conflicts of interest. Once they have verbally accepted to become members of the Task Force, a written consent form is signed as well as this "Disclosure form" and this for all Guidelines. The disclosure form must be updated if any changes occur during the elaboration to the document.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the European Society of Cardiology (ESC) Web site.

Print copies: Available from Elsevier Publishers Ltd., 32 Jamestown Road, London, NW1 7BY, United Kingdom. Tel: +44 207 424 4422; Fax: +44 207 424 4433; E-mail: gr.davies@elsevier.com

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Guidelines on the diagnosis and management of pericardial diseases. Executive summary. 2004. Electronic copies: Available in Portable Document Format (PDF) from the European Society of Cardiology (ESC) Web site.
- Diagnosis and management of pericardial disease. Pocket guidelines. Available from the ESC Web site. Also available for PDA download from the ESC Web site.
- Diagnosis and management of pericardial disease. Slide set. Available from the ESC Web site.

Print copies: Available from Elsevier Publishers Ltd., 32 Jamestown Road, London, NW1 7BY, United Kingdom. Tel: +44 207 424 4422; Fax: +44 207 424 4433; E-mail: gr.davies@elsevier.com

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on July 26, 2004. The information was verified by the guideline developer on September 24, 2004. This summary was updated on May 3, 2005 following the withdrawal of Bextra (valdecoxib) from the market and the release of heightened warnings for Celebrex (celecoxib) and other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on June 16, 2005, following the U.S. Food and Drug Administration advisory on COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI Institute on May 17, 2007 following the U.S. Food and Drug advisory on Colchicine. This summary was updated by ECRI Institute on June 22, 2007 following the U.S. Food and Drug Administration (FDA) advisory on heparin sodium injection. This summary was updated by ECRI Institute on July 12, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Troponin-1 Immunoassay. This summary was updated by ECRI Institute on March 13, 2008 following the updated FDA advisory on heparin sodium injection.

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