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2015 ESC Guidelines for the diagnosis and management of pericardial diseases – Web Addenda

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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The disclosure forms of all experts involved in the development of these guidelines are available on the ESC website http://www.escardio.org/guidelines.

Keywords Guidelines • Aetiology • Constrictive pericarditis • Diagnosis • Myopericarditis • Pericardial effusion • Pericardiocentesis • Pericarditis • Pericardium • Prognosis • Tamponade • Therapy

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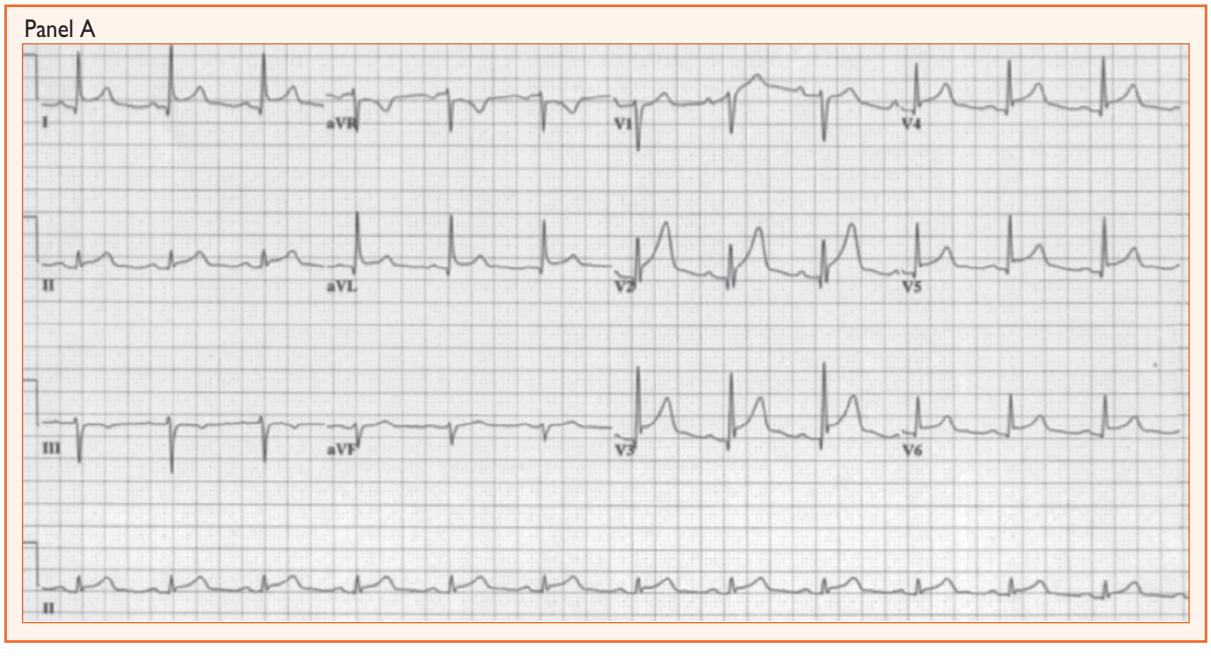
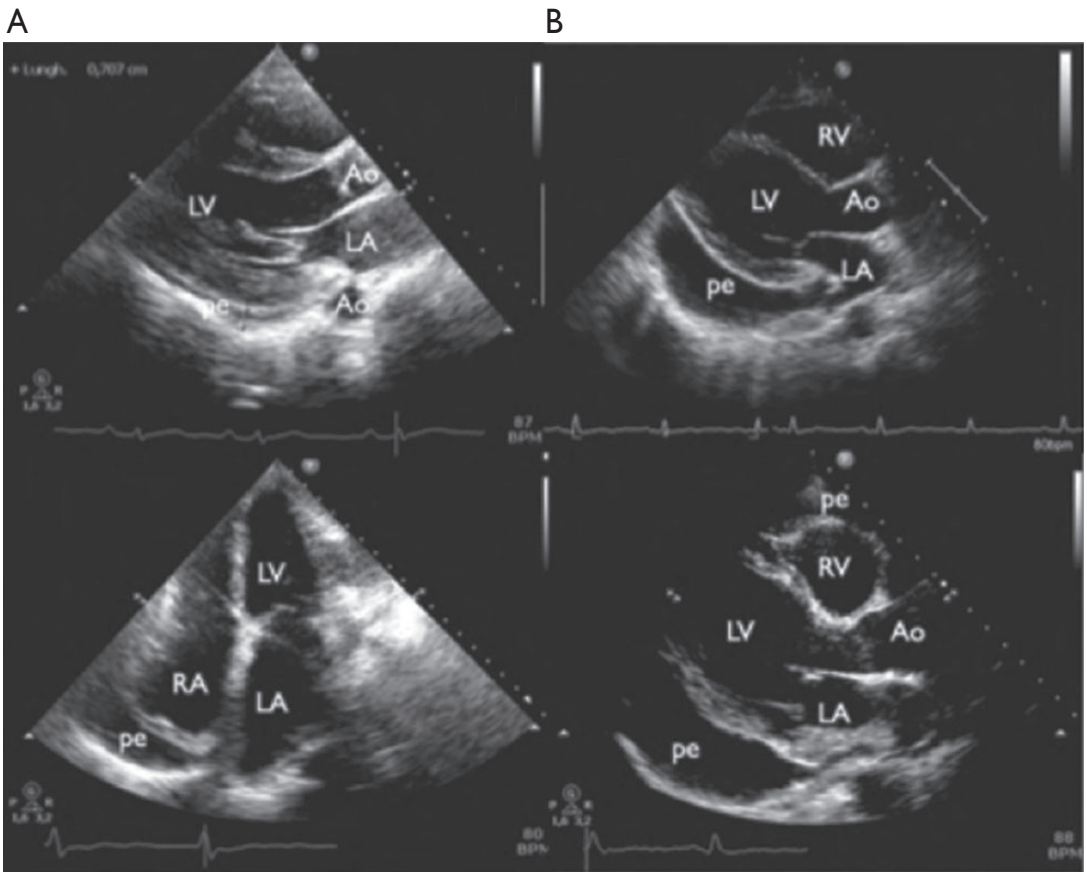
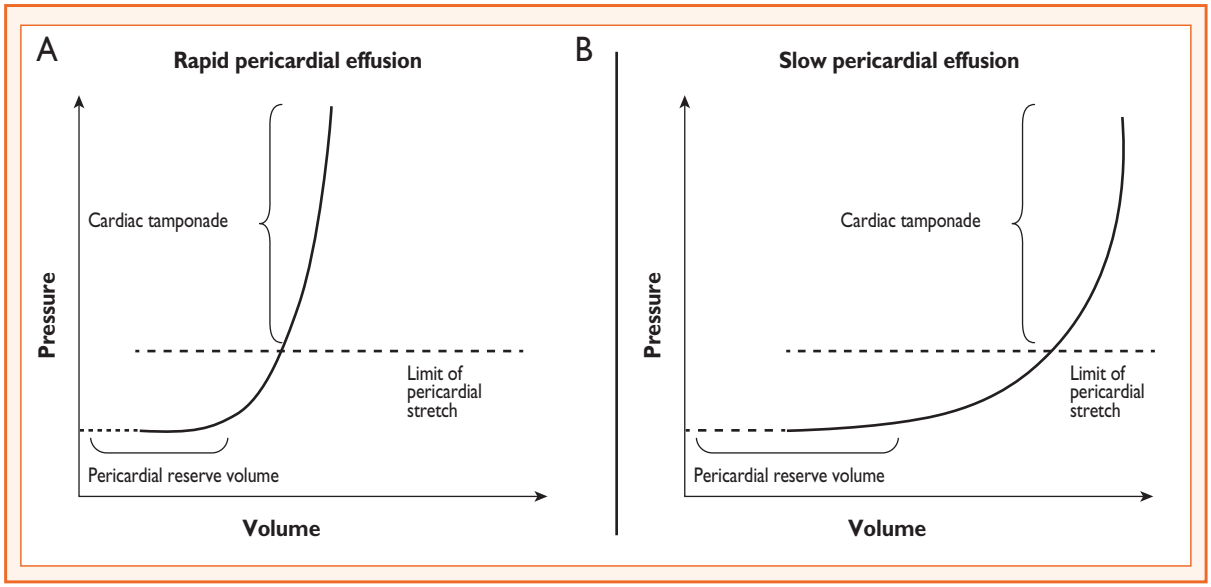


Web Figure 1 Diffuse ST elevation (typically concave up) with PR depression in some leads in a patient with acute pericarditis.[5]

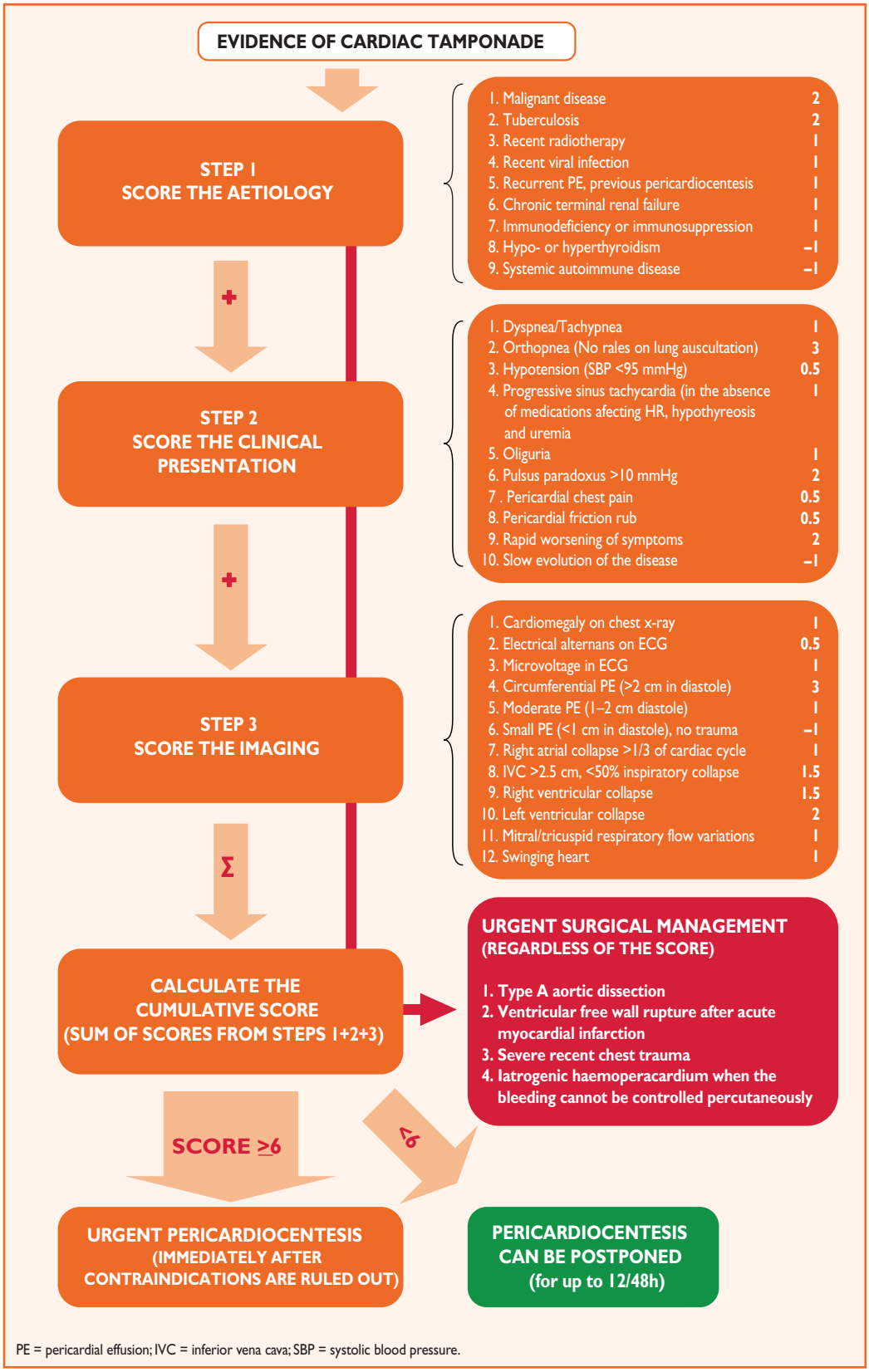


Ao = aorta; LA = left atrium; LV = Left Ventricle; pe = pericardial effusion; RV = right ventricle.

Web Figure 2 Semi-quantitative assessment of the size of pericardial effusion is based on the measure of the largest telediastolic echo-free space according to several echocardiographic views. *Panel A.* A mild pericardial effusion (<10 mm) is generally located posteriorly and adiacent to the RA. *Panel B.* In moderate (10–20 mm) and large (>20 mm) ones, the effusions become circumferential.[48]



Web Figure 3 Pressure/volume curve of the pericardium with fast accumulating pericardial fluid leading to cardiac tamponade with a smaller volume (*A*) compared with the slowly accumulating pericardial fluid reaching cardiac tamponade only after larger volumes (*B*).[48]



Web Figure 4 Triage cardiac tamponade proposed by the European Society of Cardiology Working Group on myocardial and pericardial diseases.[74]

Web Box

Aspirin and NSAIDs in pericardial diseases and concomitant use of anti-platelets and anticoagulant therapy

NSAIDs are the mainstay of the therapy of inflammatory pericardial diseases (acute and recurrent pericarditis), but are less effective or not effective at all if inflammation is absent (i.e. in some pericardial effusions with normal CRP). If tolerated, they should be used at appropriate anti-inflammatory doses during the acute episodes until complete symptom resolution and CRP normalization. Aspirin, ibuprofen and indomethacin should be used every 8 h, particularly during the acute episodes, and intravenously in sick hospitalized patients. All these agents have gastrointestinal side effects, and gastro-duodenal prophylaxis with proton pump inhibitors is recommended when they are used chronically.

Unsatisfactory results are often reported with NSAIDs. Some of these failures are due to low doses or courses that are too short, with interruption of the therapy while the disease is still active, as manifested by persistently elevated CRP. Long courses (weeks–months) until complete normalization of CRP should be considered in more difficult cases. This is particularly important during corticosteroid tapering.

The selection of specific NSAIDs should be based on physician experience and the patient's previous history (e.g. an NSAID that was effective in previous episodes should be the preferred choice) and co-morbidities. For example, aspirin is the preferred choice in patients with ischaemic heart disease or when the patient is already on aspirin or needs anti-platelet treatment;[5,6,56] doses of aspirin up to 1500 mg/day have been shown to be effective as an anti-platelet agent, and an attenuated anti-platelet efficacy at higher daily doses remains to be convincingly demonstrated.[1,2,3] If other NSAIDs are used, low-dose aspirin should not be discontinued if indicated, even though concomitant administration of the two may amplify the risk of upper gastrointestinal bleeding and might compromise the anti-platelet effects of aspirin.[4,5,6,7,8] Indomethacin and other NSAIDs should be avoided in patients with coronary artery disease; in fact, most non-aspirin NSAIDs may have a small cardiovascular risk, which was revealed in several trials and observational studies[9,10] showing that cyclo-oxygenase-2 (COX-2) inhibitors (coxibs), diclofenac, indomethacin and ibuprofen significantly increase cardiovascular risk [relative risk (RR) ~1.3], while naproxen at high doses (500 mg × 2) probably does not, perhaps due to the almost permanent inhibition of thromboxane synthesis induced in some people at these high doses.

In patients anticoagulated with warfarin, only expert opinions guide the therapy. Aspirin should be avoided unless specifically indicated (e.g. for stent implantation), colchicine use is strongly recommended, low doses of corticosteroids are often considered, low doses of NSAIDs are often used and paracetamol and analgesics may be added.

In contrast to anti-platelet therapies, concomitant use of heparin and anticoagulant therapies is often perceived as a possible risk factor for the development of worsening or haemorrhagic pericardial effusion that may result in cardiac tamponade. The use of anticoagulant therapy has also been considered a possible poor prognostic predictor in the setting of acute pericarditis, but the available evidence does not support this.[6,7] A multivariable analysis of nearly 500 consecutive cases of acute pericarditis did not show this to be the case.[9] 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]

Web Tables

Web Table 1A Aspirin and commonly used NSAIDs in pericardial diseases; main regimens in adults (for children see Web Table 7; for concomitant use of anti-platelets and anticoagulant therapy see Web box)

Drug	Usual initial dose (with possible range)	Length of treatment	Tapering
Aspirin	500–1000 mg every 6–8 hours (1,5–4 g/day).	FIRST uncomplicated episode: 1–2 weeks. RECURRENCES: 2–4 weeks up to several months. The optimal length of treatment is debatable, and CRP should be considered as a marker of disease in activity to guide management and treatment length. The need for gradual tapering (every 1–2 weeks and only if the patient is asymptomatic and CRP is normal) is recommended by this Task Force.	Decrease the total daily dose by 250–500 mg every 1–2 weeks.
Ibuprofen	600 mg every 8 hours (range 1200–2400 mg).		Decrease the total daily dose by 200–400 mg every 1–2 weeks.
Indomethacin	25–50 mg every 8 hours: start at lower end of dosing range and titrate upward to avoid headache and dizziness.		Decrease the total daily dose by 25 mg every 1–2 weeks.
Naproxen	500–1000 mg daily every 12 hours; if tolerated well and clinically indicated, may increase to 1500 mg daily of naproxen base for limited time period (<6 months). Dosage expressed as naproxen base; 200 mg naproxen base is equivalent to 220 mg naproxen sodium.		Decrease the total daily dose by 125–250 mg every 1–2 weeks.

CrCl = creatinine clearance; NSAIDs = non-steroidal anti-inflammatory drugs.
Start at lower end of dosing range and titrate upward.
According to local availability of the different agents, consider intravenous use of NSAIDs in hospitalized symptomatic patients.
Dosing: geriatric refer to adult dosing. Use lowest recommended dose and frequency
Dosing: renal impairment CrCl <30 mL/min: NSAIDs use is not recommended (for aspirin: use is not recommended if CrCl <10 mL/min)
Dosing: hepatic impairment use with caution; dose adjustment may be required.

Web Table 1B **Colchicine in pericardial diseases**

Mechanism of action	Colchicine concentrates in leucocytes and inhibits the process of microtubule self-assembly by binding b-tubulin, thus interfering with chemotaxis,degranulation, and phagocytosis.Colchicine halves the recurrences in acute pericarditis (first episode and recurrences) and is effective in the prevention of postpericardiotomy syndrome following cardiac surgery; if tolerated should be added.
Dose	Low fractionated doses improve tolerability: 0.5–0.6 mg twice daily or 0.5–0.6 mg daily for patients <70 kg or intolerant to higher doses. In patients with good tolerance a single dose of 1 mg daily might improve the compliance. A loading dose was initially used but is now avoided to reduce potential gastrointestinal side effects and improve patient compliance.
Dose adjustment according to age and renal or hepatic dysfunction	**Condition** — **Dose adjustment** Children ≤5 years — 0.5 mg/day >5 years — 1.0–1.5 mg/day in two or three divided doses Elderly (>70 years) — Reduce dose by 50% and consider CrCl Renal impairment CrCl 35–49 mL/min — 0.5–0.6 mg once daily CrCl 10–34 mL/min — 0.5–0.6 mg every 2–3 days CrCl <10 mL/min — Avoid chronic use of colchicine. Use in serious renal impairment is contraindicated by the manufacturer. Hepatic dysfunction — Avoid in severe hepatobiliary dysfunction and in patients with hepatic disease.
Major drug interactions	Macrolide antibiotics: decrease colchicine metabolism, consider colchicine dose reduction. Statins: increase the risk of myotoxicity, consider therapy modification or dose reduction. Cyclosporine: reciprocal enhancement of adverse/toxic effects, consider therapy modification or dose reduction. Verapamil: increases verapamil serum concentration, enhances colchicine nephrotoxicity, monitor therapy.
Side effects	Common side effects are gastrointestinal (up to 10% of cases) including nausea, vomiting, diarrhoea, abdominal pain, usually being a common cause of drug withdrawal; generally mild, they may resolve with dose reduction. Weight-adjusted doses may reduce these side effects. Notably diarrhoea may be exacerbated by the common concomitant use of antibiotics and proton pump inhibitors. Less common side effects include elevation of transaminases and reversible alopecia. In <1 % of cases, other side effects are reported, including bone marrow suppression and myotoxicity.
Long term use	1–2 mg/day colchicine is safe even when given continuously for decades, as learned in patients with FMF (who usually now continue this drug also in pregnancy and lactation) and in patients with Behçet's disease. In FMF patients even prolonged exposure to colchicine seems to have no effects on male or female fertility and pregnancy outcomes.
Length of therapy	In published trials colchicine has been used for 3 months after the initial episode of acute pericarditis and for 6 months after a recurrence. In recurrent more severe cases, some authors advocate a longer use of the drug: up to 12–24 months after the last recurrence, tailored to the individual patient and with gradual tapering, considering that recurrences have been described after colchicine discontinuation. Most of us prefer to discontinue it as the last drug, after having discontinued first corticosteroids and secondly NSAID.
Some practical issues	Colchicine halves, but does not eliminate all recurrences. It generally fails as monotherapy: efficacy has been demonstrated almost exclusively for combination therapy with an NSAID and/or corticosteroids. In chronic pericardial effusions with normal CRP it is generally not efficacious.

CrCl = creatinine clearance; CRP = C-reactive protein; FMF = familial Mediterranean fever; NSAID = non-steroidal anti-inflammatory drug.

Web Table 2 **Immunosuppresant and biological drugs more commonly used in recurrent pericarditis**

	Dose	Geriatric	Renal impairment	Hepatic impairement	Pediatric	Comment
Azathioprine	Initial: 1 mg/kg/day given once daily or divided twice daily, gradually increased till 2–3 mg/kg/day.	Refer to adult dosing.	No specific dose adjustments provided in manufacturer's label.	- No dose adjustments provided in manufacturer's label. - Caution, however, since possible hepatotoxicity.	- Limited data available: children and adolescents: oral: 2–2.5 mg/kg - Dose once daily.	- Haematologic and hepatic toxicity. - Allopurinol concomitant use contraindicated (severe myelosuppression) - Useful as a sparing corticosteroids Agent.
IVIG	400–500 mg/kg/day for 5 days, or 1 g/kg/day for 2 days, eventually repeated every 4 weeks.	Refer to adult dosing.	Use with caution due to risk of immune globulin-induced renal dysfunction; the rate of infusion and concentration of solution should be minimized.	No dose adjustments provided in manufacturer's label.	Refer to adult dosing.	Generally well tolerated. Expensive. Effective in the acute episode.
Anakinra	1–2 mg/kg/day up to 100 mg once daily subcutaneously.	Refer to adult dosing.	No dose adjustment required for renal impairment.	No dose adjustments provided in manufacturer's label.	1–2 mg/kg/day subcutaneously max 100 mg/day.	- Generally well tolerated. - Expensive. - Effective in the acute episode.

CrCl = creatinine clearance; IVIG = intravenous immunoglobulin.
Drugs as IVIG, anakinra or azathioprine may be considered in cases of proven infection-negative recurrent corticodependent pericarditis not responsive to colchicine, after a careful assessment by an expert multidisciplinary team including cardiologists, immunologists and/or rheumatologists. It is also mandatory to properly educate the patient and his/her caregivers about the clinical risks related to immunosuppressive drugs and the safety measures to adopt during the treatment.

Web Table 3 **Aetiologic diagnosis of moderate to large pericardial effusions according to major published series**

Feature	Corey GR *et al.*[74]	Sagrista-Sauleda J *et al.*[75]	Levy PY *et al.*[76]	Reuter H *et al.*[77]	Ma W *et al.*[78]
Patients	57	322	204	233	140
Study years	1993	1990–1996	1998–2002	1995–2001	2007–2009
Country	USA	Spain	France	South Africa	China
Effusion size	>5 mm	>10 mm	NR	NR	Moderate to large[a]
Cardiac tamponade	NR	37	NR	NR	NR
Idiopathic	7	29	48	14	9
Cancer	23	13	15	9	39
Infections	27	2	16	72	29
Connective tissue diseases	12	5	10	5	6
Metabolic	24	6	12	0	0
Iatrogenic	0	16	0	0	9

NR = not reported.
[a]all effusions requiring pericardiocentesis. Data are reported as percentages.

Web Table 4 **Major published series on constrictive pericarditis. In developed countries most cases are idiopathic, while tuberculosis is the most important cause in developing countries, where tuberculosis is endemic**

Feature	Cameron *et al.*[90]	Ling *et al.*[91]	Bertog *et al.*[92]	Mutyaba AK *et al.*[93]
Institution	Stanford University	Mayo Clinic	Cleveland Clinic	Groote Schuur Hospital
Country	USA	USA	USA	South Africa
Years	1970–85	1985–95	1977–2000	1990–2012
Patients	95	135	163	121
Cause				
Idiopathic	40 (42%)	45 (33%)	75 (46%)	6 (5%)
Post-radiation	29 (31%)	17 (13%)	15 (9%)	0 (0%)
Post-surgery	10 (11%)	24 (18%)	60 (37%)	0 (0%)
Post-infectious	6 (6%)	26 (20%)	7 (4%)	110 (91%)[a]
Connective tissue disease	4 (4%)	10 (7%)	5 (3%)	0 (0%)
Other	6 (6%)	13 (10%)	1 (1%)	5 (4%)

[a]36 patients (29.8%) had proven tuberculosis, and 74 patients (61.2%) had presumed tuberculosis.

Web Table 5 **Final aetiologic diagnosis in major published unselected series of acute pericarditis**

	Permanyer-Miralda *et al.*[129]	Zayas *et al.*[130]	Imazio *et al.*[9]	Reuter *et al.*[77]
Patients *(n)*	231	100	453	233
Years	1977–83	1991–93	1996–2004	1995–2001
Geographic area	Western Europe	Western Europe	Western Europe	Africa
Idiopathic	199 (86.0%)	78 (78.0%)	377 (83.2%)	32 (13.7%)
Specific aetiology	32 (14.0%)	22 (22.0%)	76 (16.8%)	201 (86.3%)
Neoplastic	13 (5.6%)	7 (7.0%)	23 (5.1%)	22 (9.4%)
Tuberculosis	9 (3.9%)	4 (4.0%)	17 (3.8%)	161 (69.5%)
Autoimmune or post-cardiac injury	4 (1.7%)	3 (3.0%)	33 (7.3%)	12 (5.2%)
Purulent	2 (0.9%)	1 (1.0%)	3 (0.7%)	5 (2.1%)

*See also recent reference Gouriet *et al.* about a cohort of 933 patients.[131]

Web Table 6 High risk patients: clinical predictors of a specific cause (non-viral or non-idiopathic) and of increased risk of complications for pericarditis during follow-up (recurrences, tamponade, constriction)

Major (according to multivariate analysis)
Fever >38°C
Subacute onset
Large pericardial effusion (>20 mm on echocardiography)
Cardiac tamponade
Lack of response to aspirin or NSAID after at least 1 week of therapy
Minor (according to literature review and expert opinion):
Pericarditis associated with myocarditis
Immunodepression
Trauma
Oral anticoagulant therapy

NSAID = non-steroidal anti-inflammatory drug.

Web Table 7 Aspirin and NSAIDs: recommended regimens in children with pericardial diseases

Drug	Loading dose[a]	Length of treatment and tapering
Aspirin	Contraindicated in children due to the associated risk of Reye's syndrome and hepatotoxicity.	FIRST episode: 1–4 weeks. RECURRENCES: several weeks months. The optimal length of treatment is debatable, and CRP should probably be used as a marker of disease activity to guide management and treatment length. The need for gradual tapering (every 1–2 weeks and only if the patient is asymptomatic and CRP is normal), is not well established although proposed by this Task Force.
Ibuprofen	30–50 mg/kg/24 hours divided every 8 hours; maximum: 2.4 g/day.	
Indomethacin	Children ≥2 years: oral: 1–2 mg/kg/day in 2–4 divided doses; maximum dose: 4 mg/kg/day; not to exceed 150–200 mg/day.	
Naproxen	Children >2 years: oral suspension is recommended: 10 mg/kg/day in 2 divided doses (up to 15 mg/kg/day has been tolerated); do not exceed 15 mg/kg/day	

CRP = C-reactive protein; NSAIDs = non-steroidal anti-inflammatory drugs.
[a]Start at lower end of dosing range and titrate upward.

Web Table 8 A proposed treatment scheme for medical therapy of pericarditis during pregnancy

Drug	Pregnancy		After delivery
	<20 weeks	>20 weeks	During breastfeeding
Aspirin[a] 500–750 mg every 8 hours	First choice	To be avoided	Preferably avoided
NSAID (ibuprofen, indomethacin, naproxen)	Allowed	To be avoided	Allowed
Paracetamol	Allowed	Allowed	Allowed
Prednisone 2,5–10 mg daily	Allowed[b]	Allowed[b]	Allowed[b]

NSAID = non-steroidal anti-inflammatory drug.
[a]A dose of aspirin ≤100 mg/day is not useful as anti-inflammatory therapy.
[b]Possible association with aspirin or a NSAID; prednisone and prednisolone are metabolized by the placenta into inactive 11–keto forms, and only 10% of the active drugs may reach the foetus.
Colchicine is considered contraindicated during pregnancy and breastfeeding, although in women with Familial Mediterranean Fever no adverse events on fertility, pregnancy or fetal or child development have been reported even during prolonged exposure to the drug.[24–26]

Web Table 9 Complications of pericardiocentesis and pericardial access

Related to the pericardiocentesis and epicardial access	- Inadvertent puncture of a cardiac vessel, right ventricle or liver. - Bleeding complications: Haemopericardium; hemoperitoneum; liver haematoma. - Air embolism. - Right ventricle pseudoaneurysm. - Right ventricle-to-abdomen fistula.
Related to mapping and ablation	- Pericardial effusion; delayed pericarditis and pleuritis, delayed tamponade. - Damage to epicardial vessels, coronary vasospasm, myocardial infarction. - Phrenic nerve injury damage to esophagus, vagus nerve and lungs.

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