PERICARDITIS
AN ORPHAN DIAGNOSIS IN 2021

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Cardio_Cast

OVERVIEW OF THIS PODCAST

- Medical History
- Acute and Recurrent Pericarditis
- Complicated Pericarditis
- Novel Therapies
- TB Pericarditis
- Pericarditis in Pregnancy
- Pericarditis in ESRD
- Pericarditis in Covid-19

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MEDICAL HISTORY-
THE HAIRY HEARTS OF HOARY HEROES

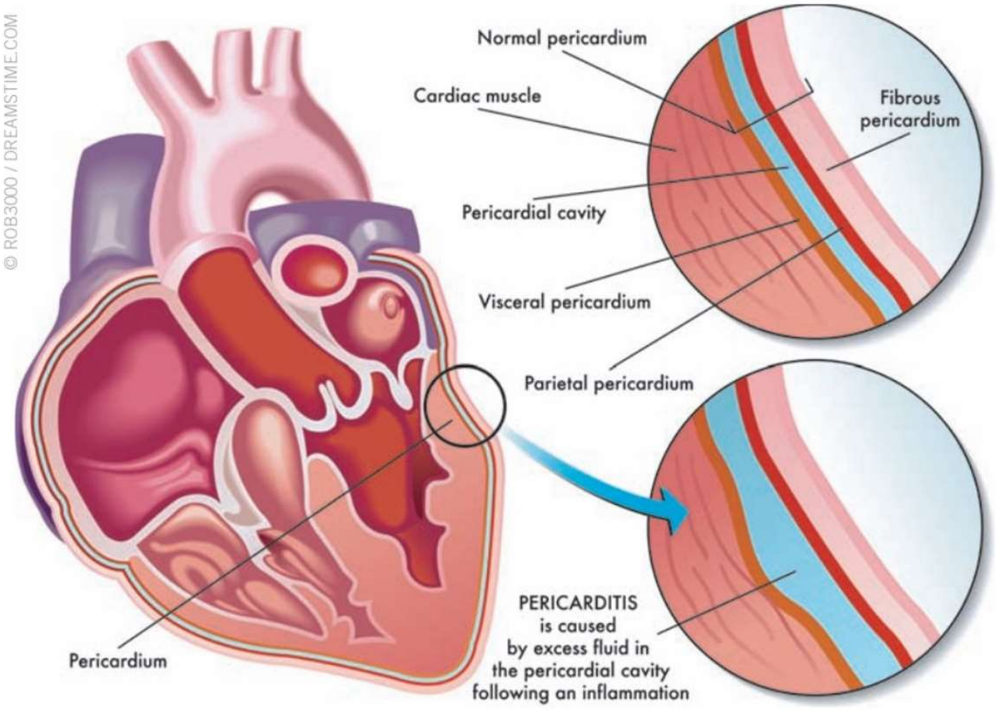
- In the ancient world animal and human sacrifices are thought to have provided most anatomic observations. Battlefields were the principal source of observations on the heart and pericardium. Hippocrates described the normal pericardium as follows: "The pericardium is a smooth mantle surrounding the heart and containing a small amount of fluid resembling urine." He did not describe pericar dial disease, primarily because Hippocratic pathology was concerned with generalized disorders but possibly also because of the ancient belief that the heart was too noble an organ to undergo a disease process. Pericardial pathology was more observable on the battlefield, and this circumstance gave rise to the widespread notion that men of valor had hair upon their hearts. Although Homer's reference to the "shaggy-haired heart" of heroes is taken by scholars to be only a poetic transference of the phrase "shaggy-haired chest", there is no mistaking this description in the straightforward Latin of Valerius Maximus.

Boyd LJ, Elias H: Contributions to diseases of the heart and pericardium. I. Historical introduction. Bull NY Med Coil 181-37. 1955
Homer: Iliad. ll:851; XVL554; 1:188-89

ACUTE AND RECURRENT PERICARDITIS

EPIDEMIOLOGY. Exact epidemiological data for acute pericarditis are lacking. The incidence was reported as 27.7 cases per 100,000 person-years in an urban area, with concomitant myocarditis in about 15% of cases. Acute pericarditis is diagnosed in 0.2% of all cardiovascular in-hospital admissions and is responsible for 5% of emergency room admissions for chest pain in North America and Western Europe.

FIGURE 1. Anatomy of the pericardium



JACC VOL. 75, NO. 1, 2020 Management of Acute and Recurrent Pericarditis JANUARY 7/14, 2020:76 – 9 2

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TABLE 1 Definitions of Pericarditis According to the Time of Presentation

	Definition
Acute	Event lasting <4 to 6 weeks
Incessant	Event lasting >4 to 6 weeks without remission
Recurrent	New signs and symptoms of pericardial inflammation after a symptom-free interval of 4 to 6 weeks
Chronic	Pericarditis lasting >3 months

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Box 1. Etiology of Pericarditis[a]

Infectious Causes

Viral (common): Enteroviruses (especially Coxsackieviruses, echoviruses); herpesviruses (especially Epstein-Barr virus, cytomegalovirus, human herpesvirus 6); adenoviruses (especially in children); parvovirus B19

Bacterial: *Mycobacterium tuberculosis* (common; other rare), *Coxiella burnetii*, *Borrelia burgdorferi*; rarely other microorganisms, usually as purulent pericarditis[b]

Fungal (rare): *Histoplasma* species (more likely in immunocompetent patients); *Aspergillus*, *Blastomyces*, and *Candida* species (more likely in immunocompromised host)

Parasitic (rare): *Echinococcus* and *Toxoplasma* species

Noninfectious Causes

Autoimmune and autoinflammatory (common)

Systemic autoimmune (especially systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, scleroderma)

Systemic vasculitides (especially eosinophilic granulomatosis with polyangiitis or allergic granulomatosis, previously named Churg-Strauss syndrome, Horton disease, Takayasu disease, Behçet syndrome)

Autoinflammatory diseases (familial Mediterranean fever, tumor necrosis factor receptor–associated periodic syndrome)

Other (sarcoidosis, inflammatory bowel diseases)

Neoplastic

Primary tumors (rare; pericardial mesothelioma)

Secondary metastatic tumors (common; lung and breast cancer, lymphoma)

Metabolic (common): Uremia, myxedema, anorexia nervosa, other rare

Traumatic and iatrogenic (common)

Early onset: Direct injury (penetrating thoracic injury, esophageal perforation); indirect injury (nonpenetrating thoracic injury, radiation injury)

Delayed onset: Pericardial injury syndromes (post–myocardial infarction syndrome, postpericardiotomy syndrome); posttraumatic, including after iatrogenic trauma (eg, coronary percutaneous intervention, pacemaker lead insertion, and radiofrequency ablation)

Drug related (rare)

Lupus-like syndrome (procainamide, hydralazine, methyldopa, isoniazid, phenytoin)

Hypersensitivity pericarditis with eosinophilia (eg, penicillins)

Pericardial and myocardial involment (eg, antineoplastic drugs: doxorubicin, daunorubicin, cytosine arabinoside, fluorouracil, cyclophosphamide)

[a] The pericardium may be affected by all categories of diseases, including infectious, autoimmune, neoplastic, iatrogenic, traumatic, and metabolic.

[b] *Pneumococcus*, *Meningococcus*, *Gonococcus*, *Streptococcus*, *Staphylococcus*, *Haemophilus*, *Chlamydia*, *Mycoplasma*, *Legionella*, *Leptospira*, and *Listeria* species and *Providencia stuartii*.

Related to management issues (for recurrences, common):

- Inappropriate dosing and/or tapering of anti-inflammatory medical therapy
- Lack of exercise restriction during the acute phase

Evaluation and Treatment of Pericarditis A Systematic Review Massimo Imazio, MD; Fiorenzo Gaita, MD; Martin LeWinter, MD

Table 1. Reported Etiology of Pericarditis in Published Series

Etiology	Reported Frequency as Percentage of Reported Cases of Pericarditis
Idiopathic[5,6,9,19,23-26]	15% (Africa) to 80%-90% (Europe and United States)
Infectious	
Viral (eg, Coxsackievirus, Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, parvovirus B19)[5,6,9,19,23-26]	Largely unknown (30%-50% in Marburg, Germany experience)
Bacterial[9,19,23-26]	
Tuberculosis	1%-4% (Italy, Spain, France), up to 70% (Africa)
Purulent	<1% (Europe) to 2%-3% (mainly Africa); rare (largely unknown)
Other infectious causes[9,19,23-26]	
Noninfectious	
Neoplastic etiology[9,19,23-27]	5%-9% to 35% (in tertiary European referral centers)
Autoimmune[9,19,23-25,a]	2%-24%
Other	Rare (largely unknown)

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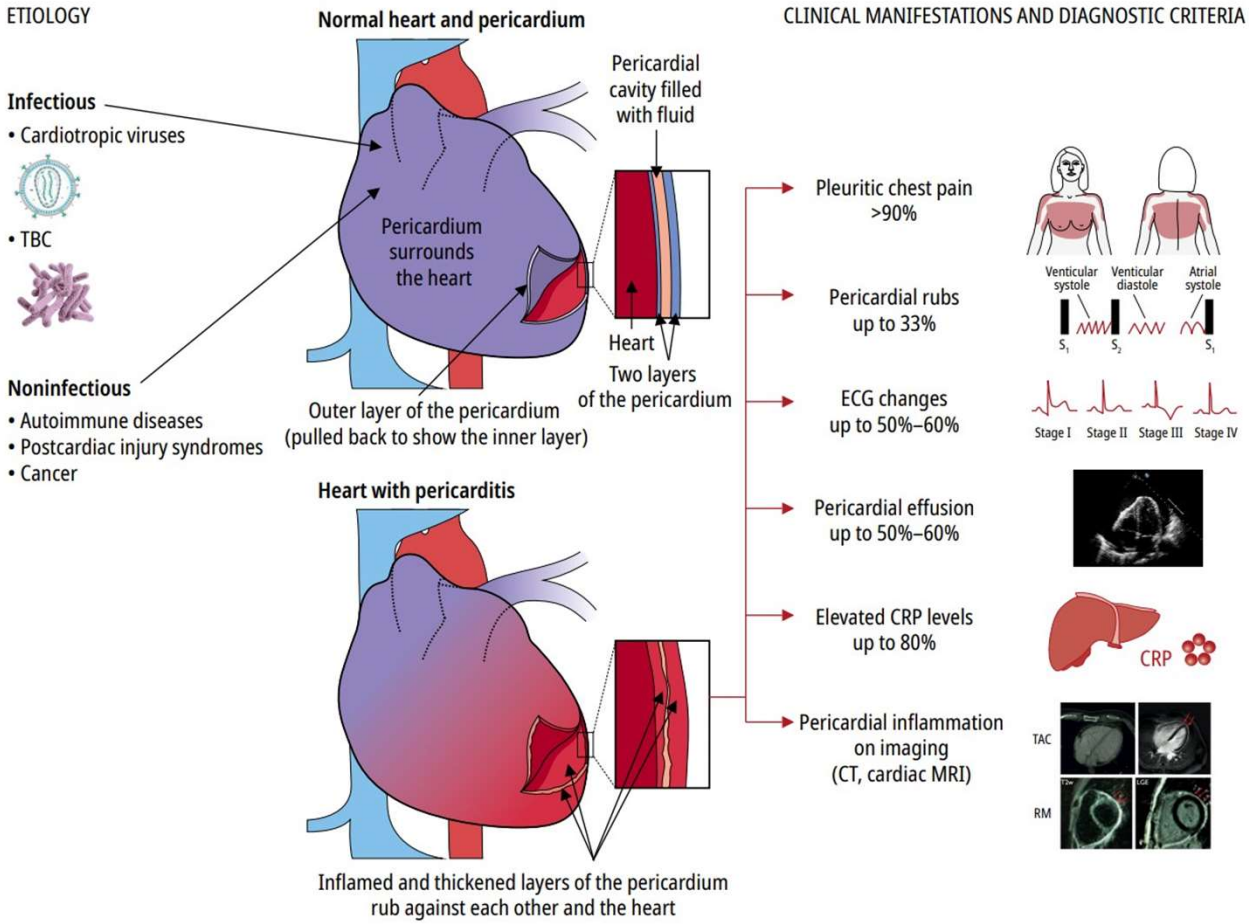

FIGURE 2 Main manifestations of pericarditis and criteria for its diagnosis
Abbreviations: TBC, tuberculosis; others, see TABLE 3

KARDIOLOGIA POLSKA 2020; 78 (5)

Table 2
Diagnostic criteria for acute pericarditis

Pericarditis	Definition and Diagnostic Criteria
Acute	Inflammatory pericardial syndrome to be diagnosed with at least 2 of the 4 following criteria: 1. Pericarditic chest pain 2. Pericardial rubs 3. New widespread ST elevation or PR depression on ECG 4. Pericardial effusion (new or worsening) Additional supporting findings: • Elevation of markers of inflammation (ie, CRP, ESR, and white blood cell count); • Evidence of pericardial inflammation by an imaging technique (computed tomography, cardiac magnetic resonance)

http://dx.doi.org/10.1016/j.ccl.2017.07.004

Box 1. History-taking for the clinical evaluation of acute pericarditis

Chest pain: central, worse lying down, or with inspiration and better sitting up/forward.

Palpitations/tachycardia (may suggest underlying myocarditis/myocardial involvement or presence of haemodynamically significant effusion).

Pre-syncope/syncope (may suggest significant associated effusion and/or myocardial involvement).

Pleuritic symptoms (may suggest concomitant pleuritis, connective tissue disease or periodic fever syndrome).

Hiccups (phrenic nerve irritation from a large pericardial effusion).

Dysphagia (oesophageal compression by large effusion; symptom of underlying malignancy or scleroderma).

Fever (may point towards bacterial infection, haematological malignancy, systemic autoimmune disease, periodic fever syndromes).

Weight loss (neoplasia, tuberculosis, systemic autoimmune disease).

Past history of cardiac surgery/thoracic trauma, autoimmune rheumatic disease, immunodeficiency.

Drugs: causative drugs (eg hydralazine), immunosuppression, oral anticoagulants.

Family history: autoimmune disease, hereditary periodic fever syndrome/recurrent pericarditis.

Table 1. Diagnostic criteria for acute pericarditis.

Diagnostic tool	Diagnostic criteria
History and physical examination	Pericardial chest pain and pericardial rub
ECG	New widespread ST elevation or PR segment depression
Echocardiography	New or worsening pericardial effusion
Blood tests	Elevated inflammatory markers such as C-reactive protein, erythrocyte sedimentation rate and white blood cell count.
Cardiac MRI or cardiac tomography	Presence of pericardial inflammation

Note: Diagnosis requires two of the following criteria.

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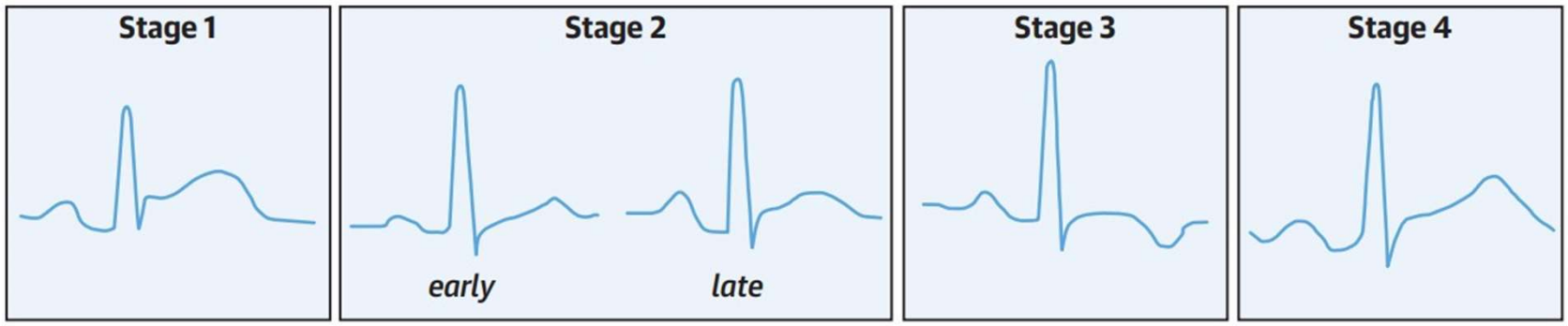
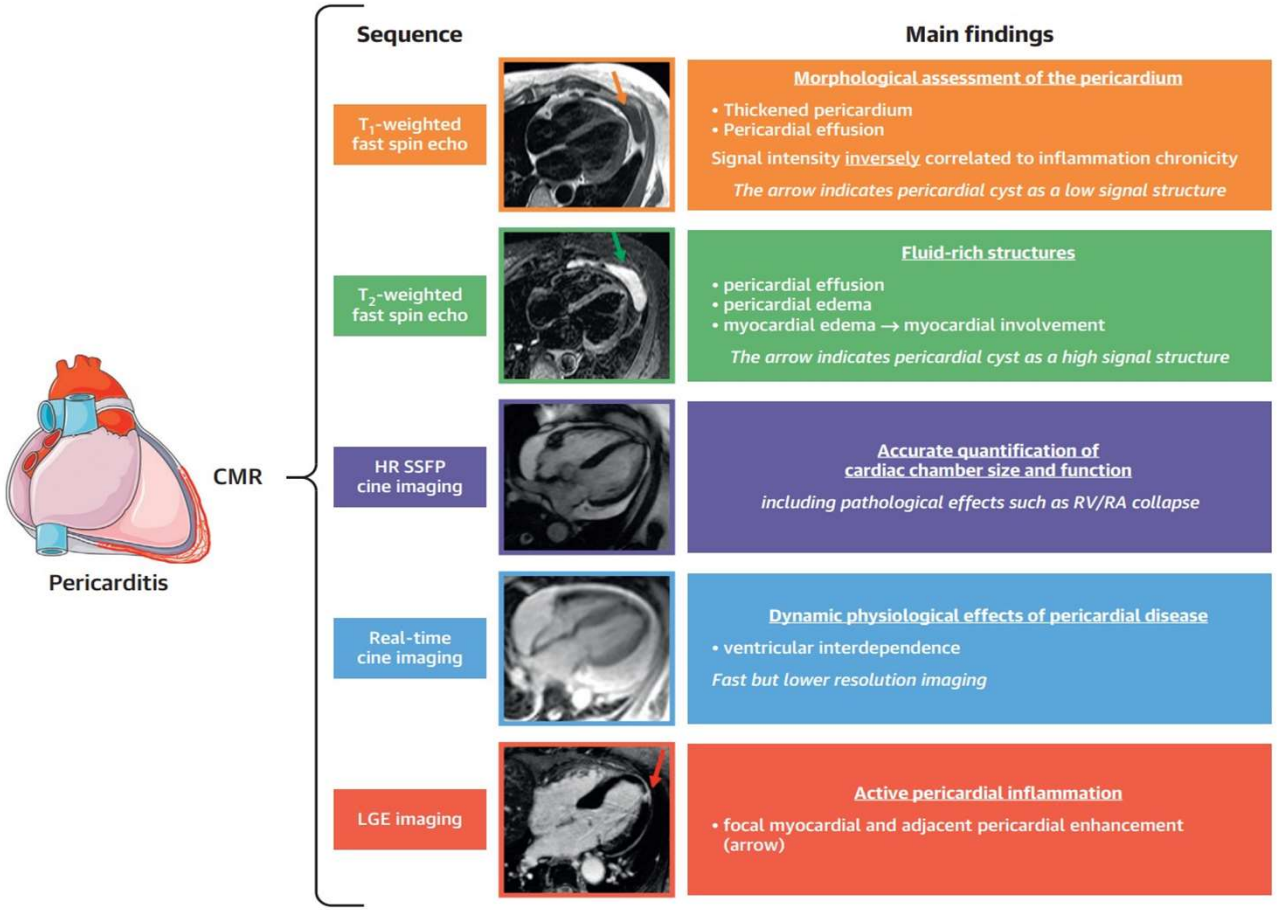
FIGURE 1 ECG Changes in Acute Pericarditis



In the first stage, a PR-segment depression and generalized ST-segment elevation are seen. The second stage is the normalization of these findings. In the third stage, a T-wave inversion predominates. The fourth stage is represented by the normalization of all of these changes. ECG = electrocardiogram.

JACC VOL. 75, NO. 1, 2020 Management of Acute and Recurrent Pericarditis JANUARY 7/14, 2020:76 – 9 2

FIGURE 2 Major Findings at CMR in Patients With Pericarditis



The different sequences acquired through cardiac magnetic resonance (CMR) can greatly help in the diagnosis of pericarditis, starting from the morphological assessment until the individuation of the area of active inflammation of the pericardium. This figure was partially created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License. CMR = cardiac magnetic resonance; HR SSFP = high-resolution steady-state-free-precession; LGE = late gadolinium enhancement; RA = right atrium; RV = right ventricle.

JACC VOL. 75, NO. 1, 2020 Management of Acute and Recurrent Pericarditis JANUARY 7/14, 2020:76 – 9 2

TABLE 2 Differential Diagnosis for Acute Pericarditis

Diagnosis	Clinical Presentation	ECG Findings	Echocardiography	Coronary Angiography	CMR	Biomarkers
Takotsubo syndrome	Chest pain, dyspnea, syncope, arrhythmias, sudden cardiac death. Usually in older female patients triggered by an emotional event or exertion.	ST-segment elevation, T-wave inversion, QTc segment prolongation.	Apical, midventricular, basal, or focal hypokinesia/ akinesia.	Absence of obstructive CAD or angiographic evidence of acute plaque rupture.	Transmural ventricular edema in the areas of ventricular dysfunction; regional wall motion abnormalities according to the anatomical patterns. No LGE.	BNP markedly elevated, troponin I/T levels mildly increased.
Myocardial infarction	Chest pain, dyspnea, arrhythmias, sudden cardiac death.	ST-segment elevation, ST-segment depression, and/or T-wave inversion.	Regional wall motion abnormalities according to epicardial coronary artery distribution.	Coronary artery disease with acute plaque rupture, thrombus formation, and coronary dissection.	Subendocardial or transmural edema at sites of wall motion abnormalities. Regional wall motion abnormalities according to epicardial coronary artery distribution. Bright LGE typically subendocardial or transmural in an epicardial coronary artery distribution.	Troponin I/T levels significantly elevated. BNP mildly increased.
Myocarditis	Chest pain, dyspnea, acute heart failure, sudden cardiac death. Usually in young or middle-aged populations, often preceded by an upper respiratory infection or enteritis.	Nonspecific ST-segment and T-wave changes (diffuse ST-segment elevation is usually seen in myopericarditis/ perimyocarditis).	Global systolic dysfunction (sometimes regional or segmental). Pericardial involvement may be also present.	Absence of obstructive CAD or angiographic evidence of acute plaque rupture.	Subepicardial basal and lateral edema. Usually global dysfunction unless regional edema/ LGE is severe. Low intensity or bright LGE is often present with a focal "patchy" subepicardial or midventricular noncoronary distribution.	Troponin I/T levels significantly elevated. BNP mildly increased.
Acute pericarditis	Chest pain, with changes according to position (worse leaning back), pericardial rub, pericardial effusion.	PR-segment depression, concave ST-segment elevation, T-wave inversion.	Pericardial effusion, cardiac tamponade, constrictive physiology.	Absence of obstructive CAD or angiographic evidence of acute plaque rupture.	LGE of the pericardium. In cine imaging, constrictive physiology can be seen. Edema and LGE of myocardium is generally absent.	Troponin I/T mildly elevated at times. BNP levels generally normal

BNP = brain natriuretic peptide; CAD = coronary artery disease; CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement; QTc = corrected QT interval.

JACC VOL. 75, NO. 1, 2020 Management of Acute and Recurrent Pericarditis JANUARY 7/14, 2020:76 – 9 2

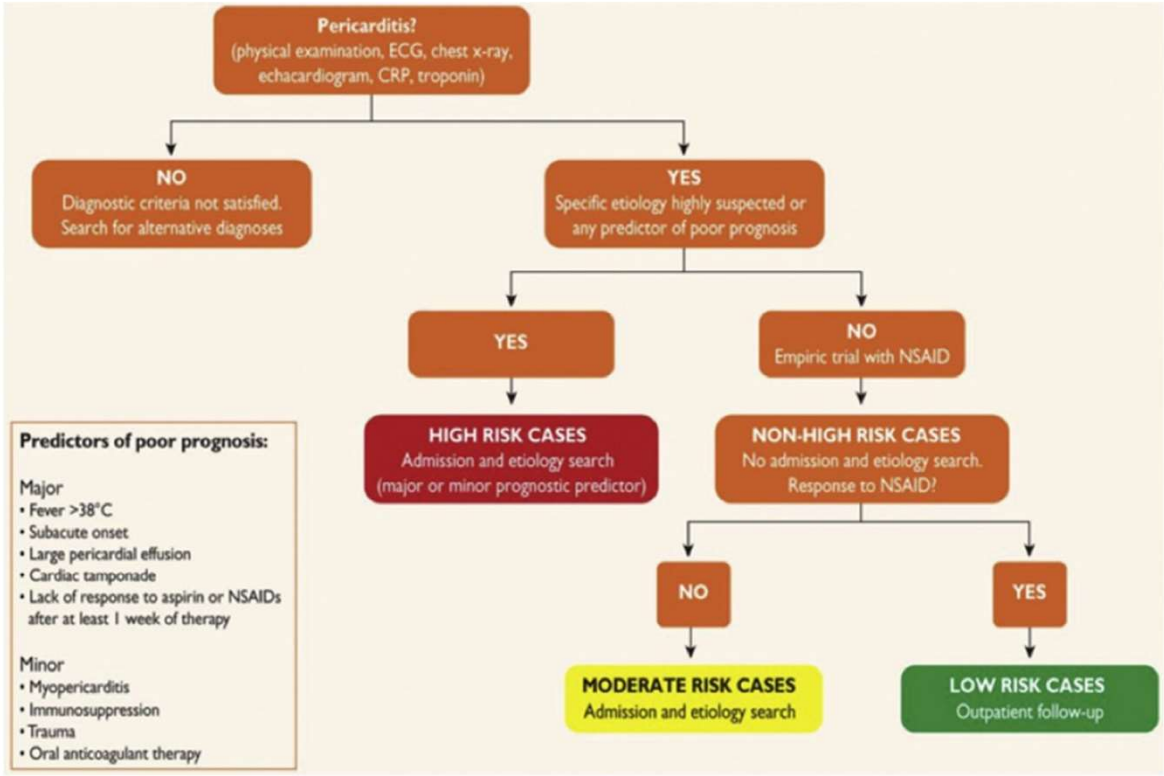


Fig. 2. Proposed triage of pericarditis according to published evidence and 2015 ESC guidelines. A large pericardial effusion is defined as an effusion with the largest telediastolic echo-free space of greater than 20 mm on echocardiography. Proposed triage of acute pericarditis according to epidemiologic background and predictors of poor prognosis at presentation (modified from Refs.[5,6,8,12]). At least one predictor of poor prognosis is sufficient to identify a high risk case. Major criteria have been validated by multivariate analysis.[9] Minor criteria are based on expert opinion and literature review. Cases with moderate risk are defined as cases without negative prognostic predictors but incomplete or lacking response to NSAID therapy. Low-risk cases include those without negative prognostic predictors and good response to anti-inflammatory therapy. Specific cause is intended as nonidiopathic cause. (*From* 2015 ESC guidelines; with permission.)

Box 1. Predictors of bad prognosis for acute pericarditis.

Major

- Temperature >38°C
- Subacute onset
- Pericardial effusion of >2.0 cm
- The presence of cardiac tamponade
- No response to aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) following a minimum of 7 days of treatment

Minor

- Myocardial involvement (myopericarditis)
- Immunocompromised patients
- Injury to pericardium/Iatrogenic
- Anticoagulation

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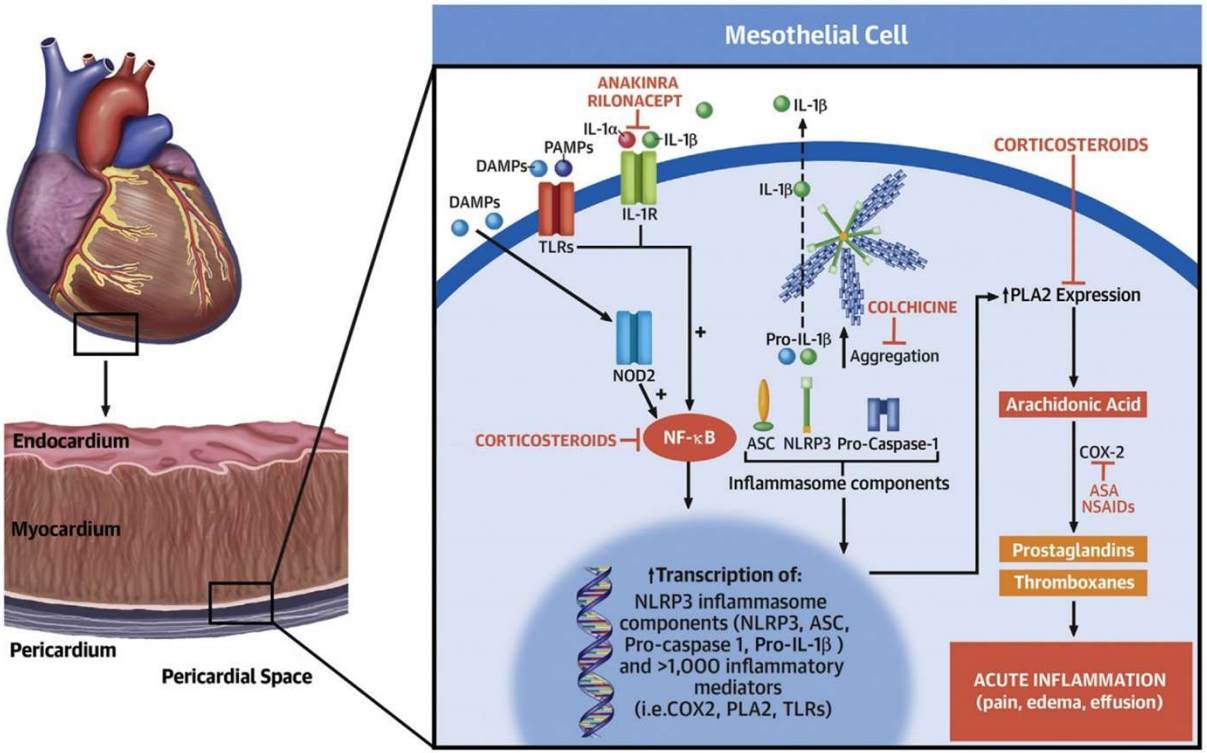
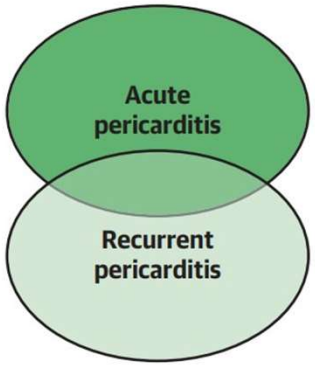
CENTRAL ILLUSTRATION **Pathophysiology of Acute Pericarditis**



Chiabrando, J.G. et al. J Am Coll Cardiol. 2020;75(1):76–92.

Injury to the pericardium leads to the release of DAMPs and PAMPs and induces NF-kB synthesis, which increases the transcription of precursors of inflammatory molecules and associated cytokines (NLRP3, ASC, pro-caspase-1) required for the polymerization of the NLRP3 inflammasome, ultimately releasing IL-1β and IL-18. NF-κB stimulates the synthesis of phospholipase-A2 required for promoting the arachidonic acid pathway and the subsequent synthesis of prostaglandins and thromboxanes. The IL-1 receptor (IL-1R) occupies a central role as IL-1α functions as an alarmin or DAMP being released during tissue injury, and IL-1β is processed and released by the inflammasome leading to amplification of the process. ASA = acetylsalicylic acid; ASC = apoptosis-associated speck-like protein containing a carboxy-terminal caspase-recruiting domain; DAMP = damage-associated molecular pattern; IL = interleukin; IL-1R = interleukin-1 receptor; NF-κB = nuclear factor kappa-light-chain enhancer of activated B cells; NLRP3 = NACHT, leucine-rich repeat, and pyrin domain-containing protein 3; NOD = nucleotide-binding oligomerization domain. NSAID = nonsteroidal anti-inflammatory drug; PAMP = pathogen-associated molecular pattern; PLA2 = phospholipase A2; TLR= toll-like receptor.

FIGURE 3 Treatment for Acute and Recurrent Pericarditis and Their Complications



DRUG	DOSE	DURATION
Acute pericarditis		
Aspirin	750-1,000 mg every 8 h	1-2 weeks
Ibuprofen	600-800 mg every 8 h	1-2 weeks
Colchicine	0.5-1.2 mg in one or divided doses	3 months
Recurrent pericarditis		
Aspirin	750-1,000 mg every 8 h	Weeks-months
Ibuprofen	600-800 mg every 8 h	Weeks-months
Indomethacin	25-50 mg every 8 h	Weeks-months
Colchicine	0.5-1.2 mg in one or divided doses	At least 6 months
Prednisone	0.2-0.5 mg/kg/daily	Months
Anakinra	1-2 mg/kg/daily up to 100 mg/daily	Months
Rilonacept	320 mg once, then 160 mg weekly	Months
Azathioprine	1 mg/kg/daily up to 2-3 mg/kg/daily	Months
Methotrexate	10-15 mg weekly	Months
MMF	2,000 mg daily	Months
IVIGs	400-500 mg/kg/day	5 days

Tamponade

Pericardiocentesis

Pericardial window

Constrictive pericarditis

Active inflammation
- Yes → Anti-inflammatory therapy as first line, pericardiectomy for refractory cases
- No → Pericardiectomy

Different treatments, their dosing, and duration according to clinical presentation are summarized. IVIGs = intravenous immunoglobulins; MMF = mycophenolate mofetil.

JACC VOL. 75, NO. 1, 2020 Management of Acute and Recurrent Pericarditis JANUARY 7/14, 2020:76 – 9 2

FIGURE 4 Specific indications for administering low-to-moderate doses of corticosteroids as the second-level therapy in pericarditis. Modified from Imazio[38]
Abbreviations: ASA, acetylsalicylic acid; others, see FIGURE 1

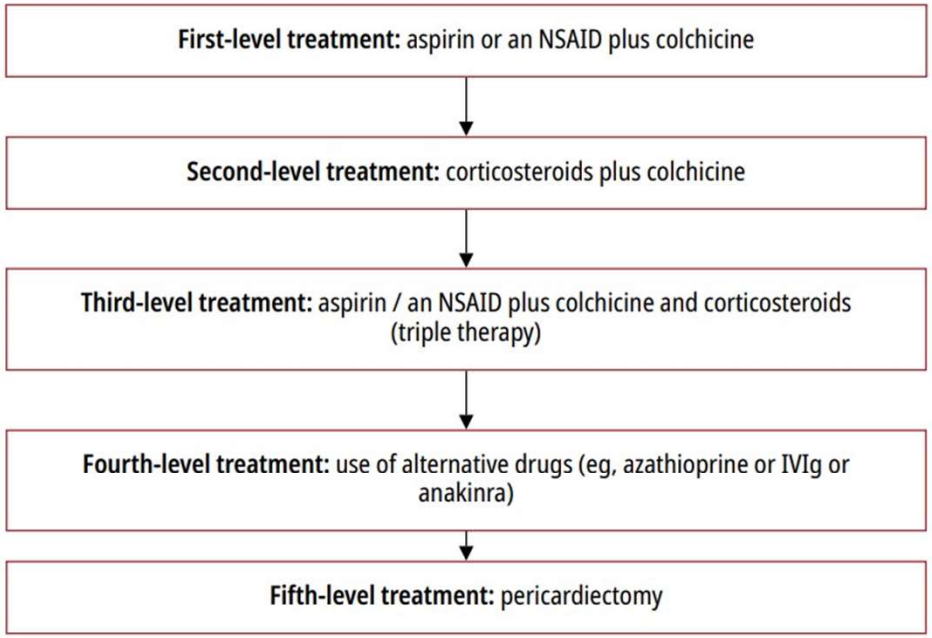
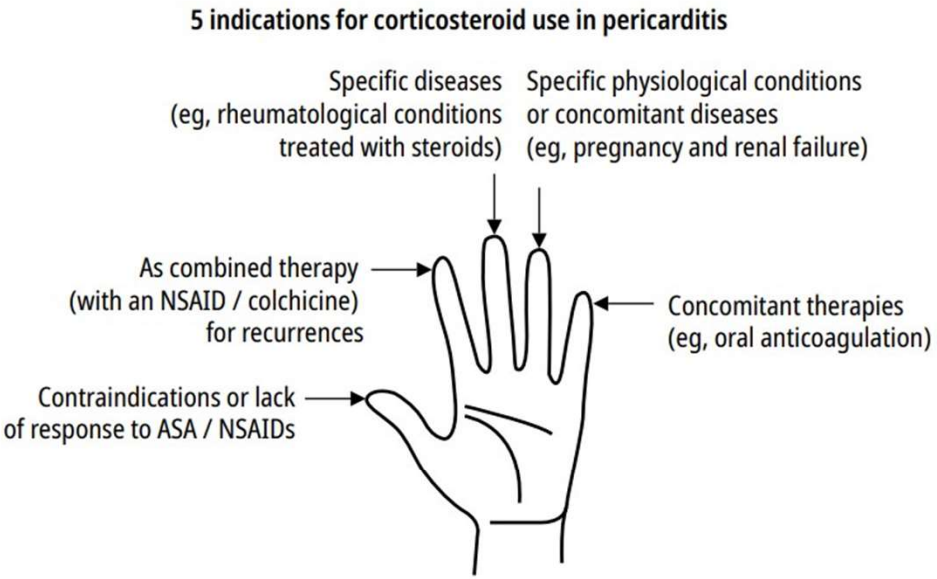


FIGURE 5 Five-level stepwise algorithm for the treatment of pericarditis, based on the current European guidelines[3] and subsequent research on the topic
Abbreviations: see FIGURE 1 and TABLE 4



KARDIOLOGIA
POLSKA 2020; 78 (5)

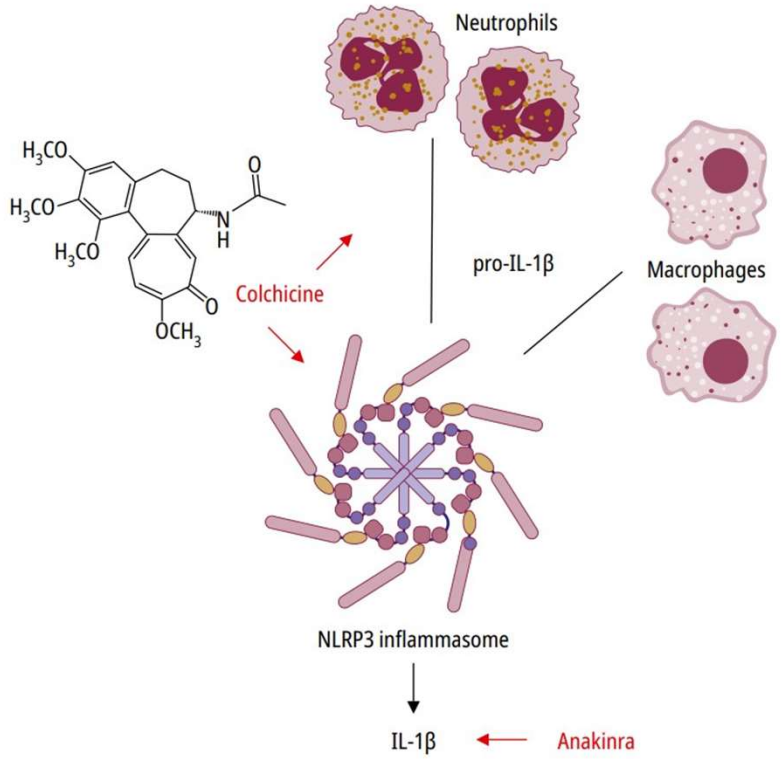


FIGURE 6 Principal mechanisms of action of colchicine and anakinra. Colchicine blocks tubulin polimerization interfering with neutrophils where it is concentrated. Moreover, it is a nonspecific inhibitor of the NLRP3 inflammasome (a cytoplasmatic complex of proteins assembled and activated by inflammatory states responsible for the activation of prointerleukin 1). Anakinra is an antagonist for interleukin-1 beta (IL-β1; the activated form of prointerleukin 1).
Abbreviations: pro-IL, prointerleukin; others, see TABLE 4

Table 1. Practical prescribing of colchicine for acute pericarditis

Patient weight	**<70 kg**	**>70 kg**
Standard dosing	500 µg once per day for 3/12	500 µg twice per day for 3/12
Dose if gastrointestinal intolerance develops[a]	250 µg once per day or 500 µg on alternate days	500 µg once per day

Cautions	**Contraindications**
Baseline blood abnormalities, especially leucopenia	Pregnancy (advise use of effective contraception)
Liver impairment	Breastfeeding
Renal impairment	Blood dyscrasias
For eGFR 15–30 mL/min/1.73 m^2 dose 500 µg every 2–3 days with caution and close monitoring; for moderate renal impairment (30–60 mL/min/1.73 m^2), reduce dose/interval as for gastrointestinal intolerance	Severe renal impairment (eGFR <15 mL/min/1.73 m^2) – avoid
	Dialysis – avoid, not removed by dialysis
Gastrointestinal disorders	Severe hepatic impairment
Cardiovascular disease	Concomitant therapy with potent CYP3A4 inhibitor or P-glycoprotein inhibitor, especially if concomitant renal or hepatic impairment.
Elderly/frail patients	

Interactions (which can significantly boost drug levels)	
P-glycoprotein inhibitors	**CYP3A4 inhibitors**
Azithromycin	Macrolides eg clarithromycin
Verapamil	Triazole antifungals eg itraconazole, ketoconazole, posaconazole
Diltiazem	
Dihydropyridines	HIV-protease inhibitors eg ritonavir
Quinidine	*Other significant interactions*
Amiodarone	Statins and fibrates (risk of rhabdomyolysis)
Ciclosporin	
Proton pump-inhibitors	
Paroxetine	
Sertraline	

[a] = Colchicine may induce a degree of acquired lactose intolerance which may in part be responsible for diarrhoea.[9] A lactose-free diet may help some patients together with dose reduction as advised above. Lactose is also a common excipient. Colchicine may also impair vitamin B12 absorption; eGFR = estimated glomerular filtration rate.

TABLE 3 Randomized Clinical Trials in Acute and Recurrent Idiopathic Pericarditis With Colchicine Added to Aspirin

Trial (Year)	Indication	Blinding	Patients	Treatment Duration	Primary Endpoint	Results
COPE trial (2005)	Acute pericarditis	No	120 patients	3-4 weeks (A), 3 months (A + C)	Recurrence	33.3% in A vs. 11.7% in A + C (P = 0.009)
CORE trial (2005)	Recurrent pericarditis	No	84 patients	3-4 weeks (A), 6 months (A + C)	Recurrence	50.6% in A vs. 24% in A + C (P = 0.02)
CORP trial (2011)	Recurrent pericarditis	Yes	120 patients	A/Ib: 3-4 weeks; Pl or C: 6 months	Recurrence	55% in A vs. 24% in A + C (P < 0.001)
ICAP trial (2013)	Acute pericarditis	Yes	240 patients	A/Ib: 3-4 weeks; Pl or C: 3 months	Incessant or recurrent pericarditis	37.5% in A vs. 16.7% A + C (P < 0.001)
CORP-2 trial (2014)	Recurrent pericarditis (2 or more events)	Yes	240 patients	A/Ib/In: 3-4 weeks; Pl or C: 6 months	Recurrence	42.5% in A vs. 21.6% in A + C (P = 0.0009)
CAFE-AIP trial (2019)	First episode of acute pericarditis (not secondary to cardiac injury or connective tissue disease)	No	110 patients	Group 1: A/Ib/In: 3-4 weeks; group 2: A/Ib/In: 3-4 weeks + C: 3 months	Recurrence	13.5% in A/Ib/In vs. 7.8% in A/Ib/In + C (P = 0.34)

A = aspirin; C = colchicine; CAFE-AIP = Colchicine Administered in the First Episode of Acute Idiopathic Pericarditis; COPE = COlchicine for acute PEricarditis; CORE = COlchicine for REcurrent pericarditis; CORP = Colchicine for Recurrent Pericarditis; CORP-2 = Efficacy and Safety of Colchicine for Treatment of Multiple Recurrences of Pericarditis; Ib = ibuprofen; ICAP = Investigation on Colchicine for Acute Pericarditis; In = indomethacin; Pl = placebo.

JACC VOL. 75, NO. 1, 2020 Management of Acute and Recurrent Pericarditis JANUARY 7/14, 2020:76 – 9 2

TABLE 2. Pharmacotherapy of acute and recurrent idiopathic (viral) pericarditis[2-7,13-20,22,25]

Pharmaco-therapy	Initial dosing	Duration (depending on response)	Tapering*
Aspirin	**Acute and recurrent:** 750-1,000 mg orally every 8 hours to a maximum of 4,000 mg/day	**Acute:** 1-2 weeks **Recurrent:** Weeks to months	250-500 mg every 1-2 weeks
Ibuprofen	**Acute and recurrent:** 600 mg orally every 8 hours to a maximum of 3,200 mg/day	**Acute:** 1-2 weeks **Recurrent:** Weeks to months	200-400 mg every 1-2 weeks
Indomethacin	25 mg orally every 8 hours to a maximum of 150 mg/day. Titrate to 50 mg orally every 8 hours as tolerated to avoid dizziness or headache	Weeks to months	25 mg every 1-2 weeks
Ketorolac	**Acute and recurrent:** 60 mg once IM (30 mg once IV) or 30 mg IV or IM every 6 hours to a maximum of 120 mg/day or 60 mg/day in patients age 65 years and older, patients weighing less than 50 kg, or those with elevated serum creatinine	5 days	None
Colchicine	**Acute and recurrent:** • For patients weighing less than 70 kg: 1.2-1.8 mg for 1 dose, then 0.6 mg orally daily*** • For patients weighing 70 kg and more: 1.2-1.8 mg for 1 dose, then 0.6 mg orally twice daily***	**Acute:** 3 months **Recurrent:** 6 months minimum	Not required
Prednisone	**Acute:** Not recommended **Recurrent:** 0.25-0.5 mg/kg/day	Dependent on symptom duration and hs-CRP	Based on starting dose: • >50 mg: decrease by 10 mg/day every 1-2 weeks • 25-50 mg: decrease by 5-10 mg/day every 1-2 weeks • 15-25 mg: decrease by 2.5 mg/day every 2-4 weeks • <15 mg: decrease by 1.25-2.5 mg/day every 2-6 weeks
Anakinra	**Recurrent:** 1-2 mg/kg subcutaneous daily to a maximum of 100 mg/day; administer every other day in patients with creatinine clearance less than 30 mL/min	8-9 months	Consider gradual tapering over a 10-month period
Azathioprine	**Recurrent:** 1.5-2.5 mg/kg orally daily	14-15 months	None
Ig	**Recurrent:** 400-500 mg/kg/day IV	5 days	None

*Tapering should only occur if patient is asymptomatic and CRP has normalized. Consider slower tapering for patients with recurrent pericarditis.
**Consider in cases of contraindication/failure of first-line therapy and when infectious cause has been excluded, or when a specific indication exists.

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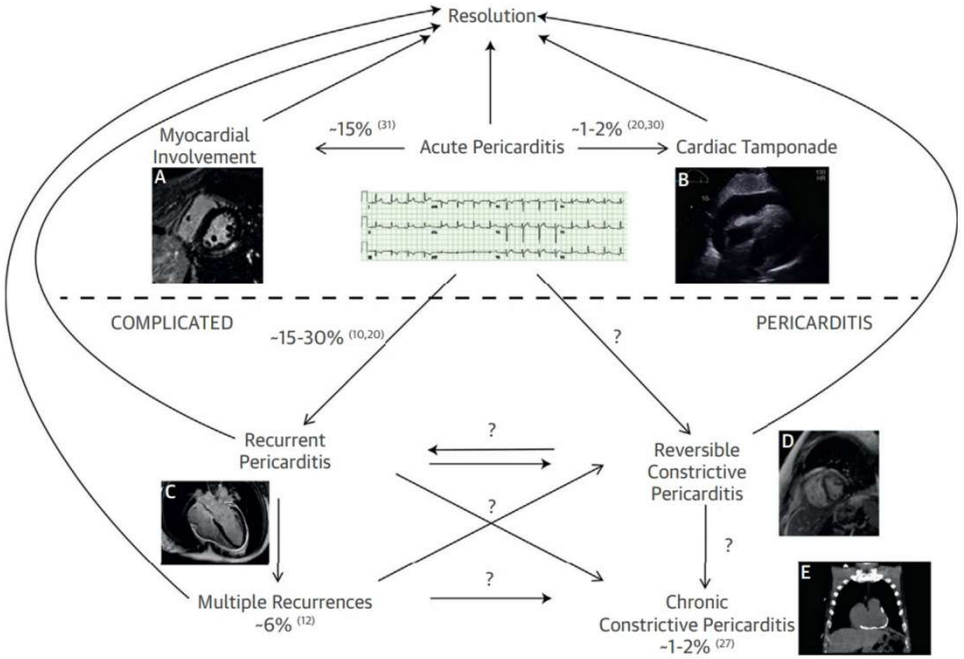
COMPLICATED PERICARDITIS

FIGURE 1 Incidence of Short-Term Adverse Events and Complicated Disease After an Episode of Acute Pericarditis



After an episode of acute pericarditis, a minority of patients will develop short-term adverse events, including cardiac tamponade or concomitant myocarditis. Delayed enhancement imaging may delineate associated subepicardial myocardial involvement **(A)**, and transthoracic echocardiography quickly defines the extent of a pericardial effusion **(B)**. With appropriate treatment of acute pericarditis, the long-term prognosis is generally good. However, a subset of patients will develop complicated pericarditis, and a few of these patients will have multiple recurrences. In select cases, delayed enhancement imaging is useful and may demonstrate increased pericardial signal **(C)**. Rarely, patients will develop chronic constrictive pericarditis requiring pericardiectomy, although the incidence of reversible constrictive pericarditis is unknown. Early inspiratory septal shift may aid in the diagnosis of constrictive pericarditis **(D)** (Online Videos 1, 2, 3, and 4), and the extent of calcification can be defined with computed tomography **(E)**.

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Cremer et al. NOVEMBER 29, 2016:2311 – 2 8

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TABLE 1 Risks for Developing Complicated Disease After an Episode of Acute Pericarditis

Treatment-related variables with increased risk in multivariable models
Corticosteroid use
Lack of colchicine
Patient-related variables with increased risk in multivariable models
Incomplete response to NSAIDs
Elevated high-sensitivity C-reactive protein
Patient-related variables without increased risk in multivariable models
Younger age
Sex
Pericardial effusion

Adapted from data in Imazio et al. (20) and Imazio et al. (33).
NSAID = nonsteroidal anti-inflammatory drug.

CENTRAL ILLUSTRATION **Complicated Pericarditis: Clinical Stages of Pericarditis With Imaging and Treatment Considerations**

Clinical Stages of Pericarditis With Imaging and Treatment Considerations

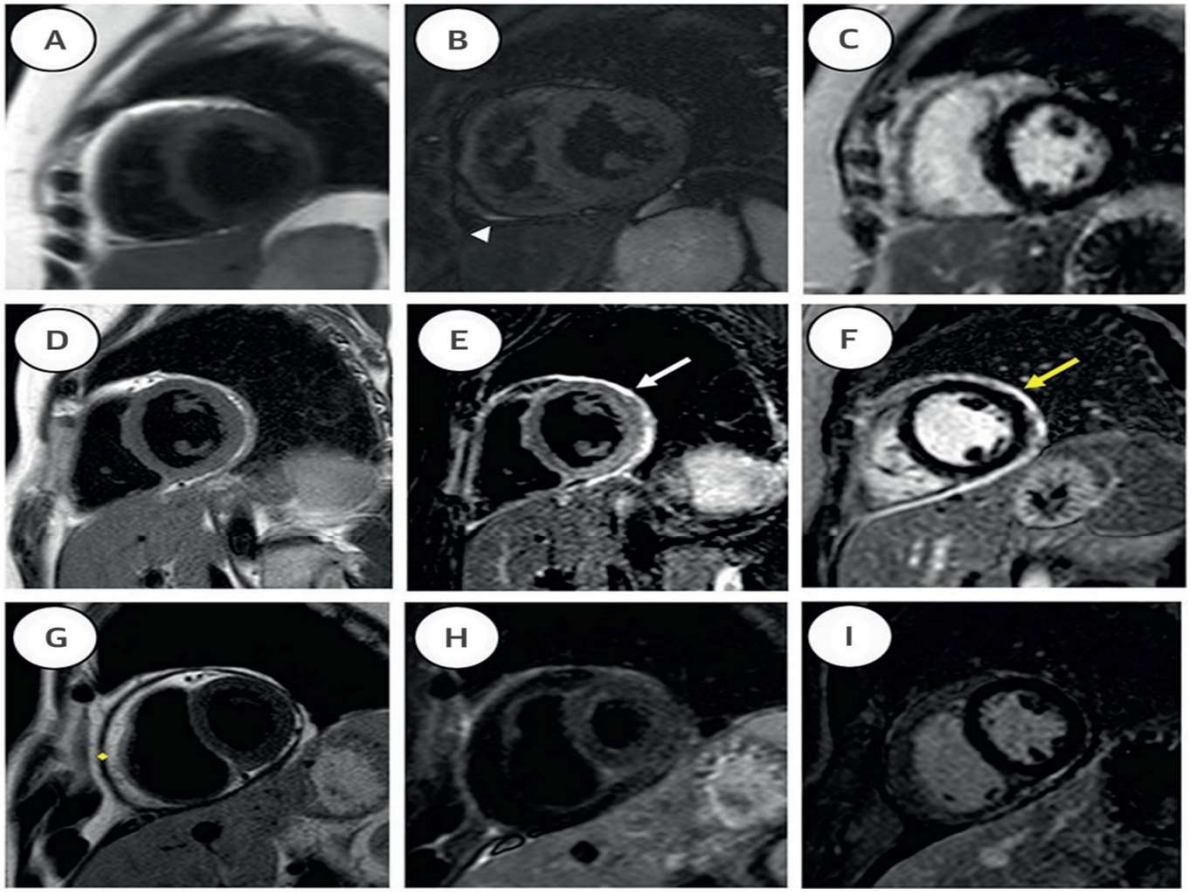
Stage of pericarditis	Acute	First recurrence	Multiple recurrences	Colchicine-resistant or steroid dependent	Constrictive
Imaging 	• Echocardiogram for pericardial effusion, myocardial involvement, constriction	• Echocardiogram for constriction • CMR in select cases for pericardial inflammation or constriction	Same as for "first recurrence"	Same as for "first recurrence"	Same as for "first recurrence" Plus possible CT for extent of calcification and preoperative planning
Treatment 	• NSAIDS (weeks) • Colchicine (3 mos.)	• NSAIDS (wks–mos.) • Colchicine (≥6 mos.)	• NSAIDS + Colchicine + Prednisone (>6 mos., taper steroid as tolerated) • Consider steroid-sparing agent (warrants further study)	• NSAIDS + Colchicine + Prednisone + Steroid-sparing agent (>6–12 mos., taper steroid as tolerated) • Consider pericardiectomy (warrants further study)	• Intensify medical therapy if inflamed • Pericardiectomy if "burnt out"

Cremer, P.C. et al. J Am Coll Cardiol. 2016;68(21):2311-28.

All patients with acute pericarditis should have an echocardiogram for short-term risk stratification, and subsequent echocardiograms can be performed if there is concern for constrictive pericarditis. In recurrent pericarditis, CMR imaging has an emerging role to assess for pericardial inflammation if the clinical evaluation is equivocal and to assess for constrictive pathophysiology if the echocardiogram is indeterminate. CT is primarily employed to assess pericardial calcification and for pre-operative planning. The mainstay of treatment is NSAIDs and colchicine with the addition of low-dose corticosteroids in patients with multiple recurrences. Steroid-sparing agents can be added in refractory cases. Early use of steroid-sparing agents and pericardiectomy for recurrent pericarditis may be beneficial and warrants further study. CMR = cardiac magnetic resonance; CT = computed tomography; LV = left ventricle; NSAID = nonsteroidal anti-inflammatory drug; RV = right ventricle.

JACC VOL. 68, NO. 21, 2016
Cremer et al. NOVEMBER 29, 2016:2311 – 2 8

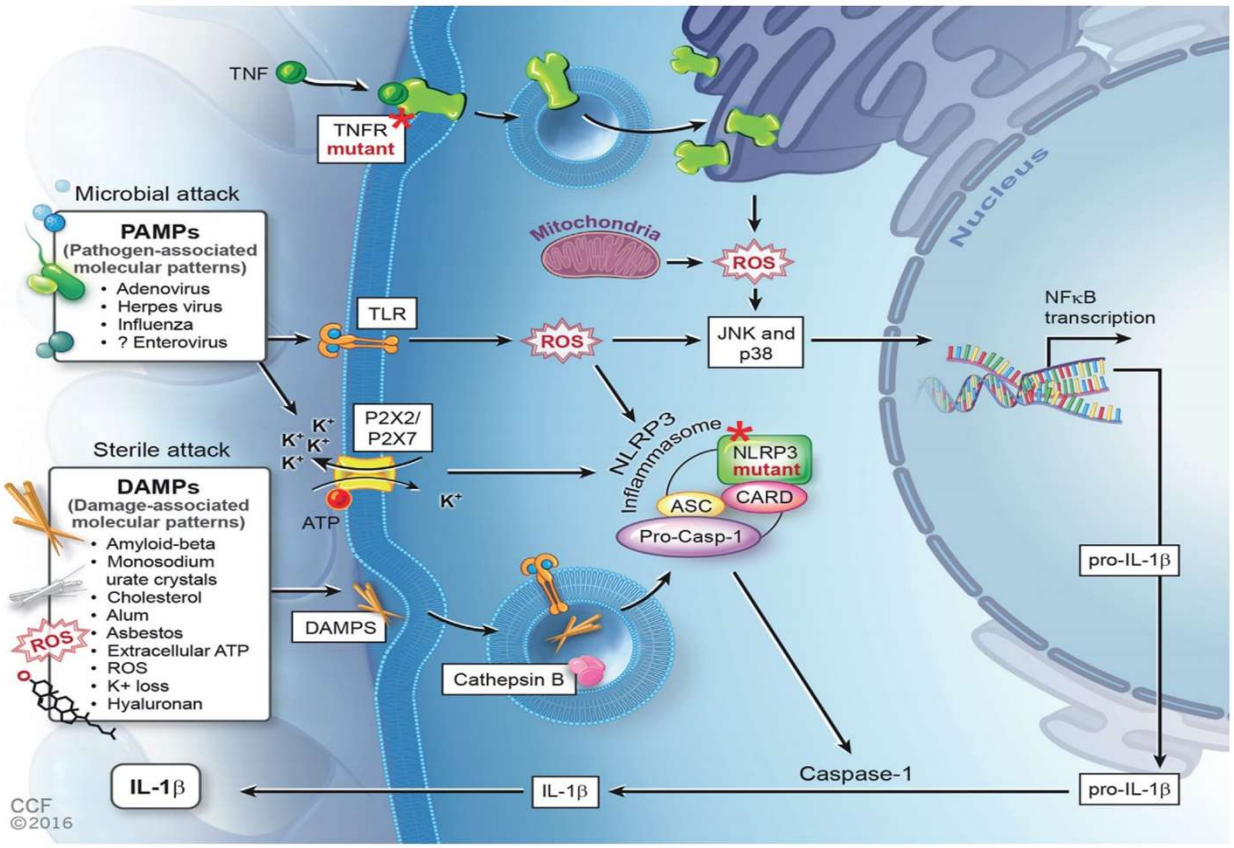
FIGURE 2 Cardiovascular Magnetic Resonance of the Pericardium



In a patient with a normal pericardium **(A to C)**, the pericardium is often difficult to delineate, even on a breath-hold double inversion-recovery, dark-blood, short-axis image **(A)**. With an edema-weighted, short-tau inversion recovery, fast spin-echo image, a hyperintense signal is seen only in the area of a trivial pericardial effusion at the inferior margin over the anterior right ventricle **(B, white arrowhead)**. With a phase-sensitive inversion-recovery technique and no fat suppression, there is no delayed pericardial enhancement **(C)**. In this patient with active pericarditis **(D to F)**, abnormal pericardial thickness is not seen **(D)**, but there is diffuse hyperintense signal on edema-weighted imaging **(E, white arrow)**, and near circumferential delayed enhancement of the pericardium **(F, yellow arrow)**. Finally, in this patient with chronic constrictive pericarditis **(G to I)**, the pericardium is abnormally thickened **(G, yellow diamond)**. There is no hyperintense signal on edema-weighted imaging **(H)**, and in this image with a fat suppression preparation, there is no delayed pericardial enhancement **(I)**.

JACC VOL. 68, NO. 21, 2016
Cremer et al. NOVEMBER
29, 2016:2311 – 2 8

FIGURE 6 Activation of the Inflammasome, a Proposed Pathogenic Mechanism in Recurrent Idiopathic Pericarditis



The initial stimulus can be either microbial (PAMPs) or sterile (DAMPs). This stimulus is then recognized by innate immunity receptors found either at the cell surface (TLRs) or inside the cell (NLRs). NLRs are then integrated into the structure of the inflammasome. Variants in the genes encoding inflammasome proteins can render them constitutively active or lower the threshold upon which the macromolecular structure is assembled in response to DAMPs and PAMPs. TLR signaling also leads to NF-κB activation and IL-1β production via ROS. Once primed by signals such as ATP, the threshold may be lower for inflammasome activation, resulting in recurrent attacks. ATP = adenosine triphosphate; CARD = caspase activation and recruitment domain; DAMPs = damage-associated molecular patterns; IL = interleukin; JNK = Jun amino-terminal kinase; K+ = potassium ions; NF-κB = nuclear factor-kappa B; NLRP3 = nucleotide-binding oligomerization domain-like receptor pyrin domain-containing 3; PAMPs = pathogen-associated molecular patterns; ROS = reactive oxygen species; TLR = Toll-like receptors; TNF = tumor necrosis factor; TNFR = tumor necrosis factor receptor.

JACC VOL. 68, NO. 21, 2016
Cremer et al. NOVEMBER
29, 2016:2311 – 2 8

TABLE 3 Emerging Therapies for Steroid-Dependent and Colchicine-Refractory Pericarditis

Therapy	Initial Dosing	Duration
Azathioprine	Started at 1 mg/kg/day, then gradually increased to 2 to 3 mg/kg/day	At least 6 months
Human immunoglobulins	400 to 500 mg/kg/day iv daily for 5 days	5 days, possibly repeated course
Anakinra	1 to 2 mg/kg/day up to 100 mg/day in adults	At least 6 months
Pericardiectomy	Not applicable	Not applicable

iv = intravenous.

Table 2 Novel immunotherapies for recurrent pericarditis

	Initial dose	Tapering	Side effects	Pediatric population	Pregnancy	Available evidence	Price/vial
Anakinra	RRP or post-pericardiotomy RP: 1–2 mg/kg/daily up to 100 mg/daily [23]	Gradual tapering is suggested after 6 months (e.g. −100 mg/week every month till 300 mg/weekly, and then −100 mg/week every 2–3 months). Continue concomitant colchicine therapy, avoid corticosteroids [23]	Local reaction at the injection site; asymptomatic elevation of transaminases [23, 24]	Children with IRP have been treated successfully with anakinra [25, 26] Dose: 1–2 mg/kg/day (up to 100 mg/day). Overall, no serious side effects were observed in this patient population [27]	No data on the efficacy and safety of IL-1 inhibitors during pregnancy	Case series; Case reports; RCT (AIRTRIP trial) [24] The IRAP (International Registry of Anakinra for Pericarditis) study [28]	54 $
Canakinumab	Recurrent rheumatic disease-associated pericarditis: 150 mg/month [29]	Not reported	Not reported	One case report of unsuccessful use of canakinumab in a child with IRP [30] One case report of successful treatment with canakinumab in a child with IRP [27]	No data on the efficacy and safety of IL-1 inhibitors during pregnancy	Case report; Case series	16.000 $
Rilonacept	RRP or post-pericardiotomy RP: 320 mg once, then 160 mg weekly	Not reported	Local reaction at the injection site, skin abscess, chest pain [31]	Not available	No data on the efficacy and safety of IL-1 inhibitors during pregnancy	A multicenter phase 2 clinical trial	6000 $

https://doi.org/10.1007/s11886-020-01308-y

TUBERCULOUS PERICARDITIS

Table 1 Stages of tuberculous pericarditis

Stage 1	
• Pathological bases	Fibrinous exudation predominates; occurrence of polymorphonuclear leucytosis is first seen with relatively abundant mycobacteria. There is a loose organization of macrophages and T cells with early granuloma formation (HIV patients with low CD4 T cells with fewer granuloma due to low immune response)
• Pathological manifestations	Dry stage (the least common form seen)
• Clinical manifestation	Patients present acute pericarditis with chest pain, pericardial friction rub, and widespread ST elevation without effusion
Stage 2	
• Pathological bases	There are predominantly lymphocytic exudates with monocytes and foam cells; presence of serosanguineous effusion is seen
• Pathological manifestation	Effusive stage (most common form seen)
• Clinical manifestation	(1) Patients present with features of heart failure and/or cardiac tamponade due to moderate to large pericardial effusion (2) Effusive constrictive pericarditis with coexistence of visceral constrictive pericarditis and simultaneous compressive pericardial fluid. The former become obvious following pericardial drainage
Stage 3	
• Pathological bases	At this stage, there is absorption of effusion, granulomatous caseation becomes organized and perocardial thickening occurs due to fibrin deposition of collagen, and ultimately fibrosis
• Pathological manifestation	Adsorptive stage
•Clinical manifestation	Symptoms and signs compatible with constrictive perocarditis but radiological and echocardiographic evidence of thick fibrinous fluid around the heart
Stage 4	
• Pathological bases	Constructive scarring (the fibrosing visceral and parietal pericardium contracts on the cardiac chambers). Calcification leads to encasing of the heart in a fibrocalcific skin. Diastolic filling is impeded, causing the classic syndrome of constrictive pericarditis
• Pathological manifestation	Constrictive stage
• Clinical manifestation	Constrictive pericarditis symptoms and signs predominate; and echocardiography confirms the diagnosis with no residual fluid in the pericardium

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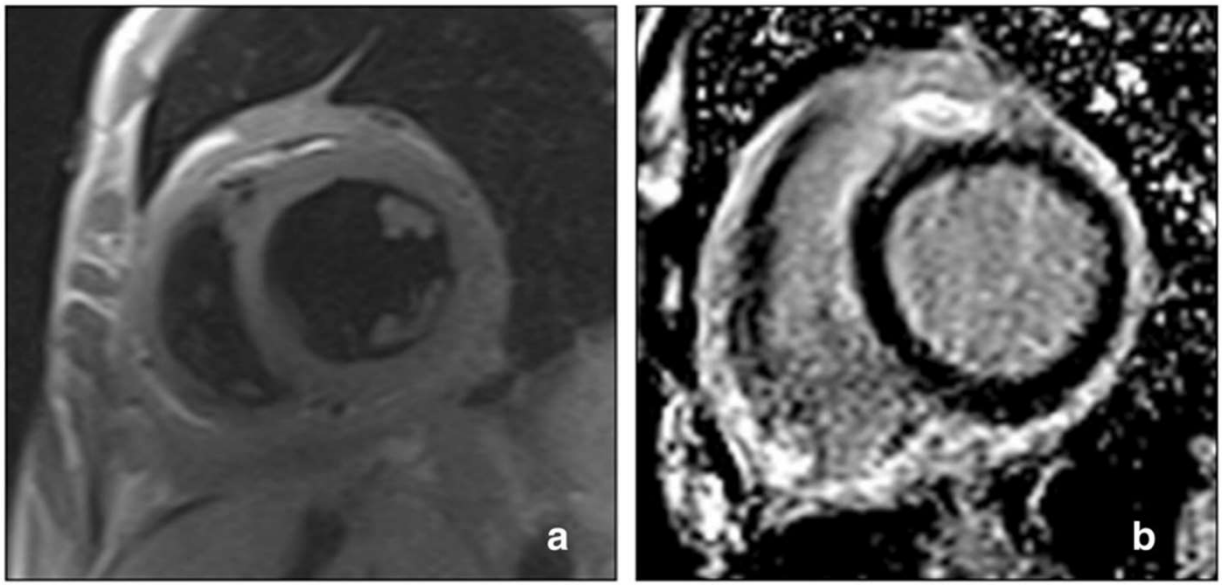

Fig. 1 Cardiac magnetic resonance images in TB pericarditis. **a** T2-weighted STIR imaging with thickened visceral and parietal pericardium. **b** Fibrotic pericardial layers after administration of gadolinium (reproduced with permission from Ntusi et al. [56])

Table 2 Diagnostic criteria for TB pericarditis in TB endemic countries

Definite TB pericarditis	Probable TB pericarditis
Tubercle bacilli are found in stained smear or culture of pericardial fluid; and/or	Evidence of pericarditis in a patient with tuberculosis demonstrated elsewhere in the body; and/or
Tubercle bacilli or caseating granulomata are found on histological examination of the pericardium	Lymphocytic pericardial exudate with elevated ADA activity; and/or
	Good response to anti-tuberculosis chemotherapy

Table created based on information from ref. [27]

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MANAGEMENT OF TUBERCULOUS PERICARDITIS

- The treatment of TBP is aimed at achieving three goals: killing and control of active Mtb; relief of the cardiac compression and adverse hemodynamic sequelae (tamponade and heart failure); and the prevention of complications of maladaptive pericardial remodeling and healing, including constrictive pericarditis.
- The goal of effective killing and control of Mtb using four anti-tuberculous drug regimens (rifampicin, isoniazid, etham butol, and pyrazinamide) for a minimum of 6 months has been the standard of care for decades in the absence of evidence of comparative effectiveness.
- Four randomized controlled trials have evaluated the role of intrapericardial and oral corticosteroids for the prevention of progression to constriction. In a recent Cochrane review of the 4 randomized trials, analysis of the cumulative data suggested that there was low certainty of evidence for a 20% reduction in all-cause mortality (risk ratio (RR) 0.80, 95% confidence interval (CI) 0.59–1.09; 660participants), compared with those who did not receive steroids in whom a significant reduction in pericarditis-related deaths was reported.

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MANAGEMENT OF IDIOPATHIC RECURRENT PERICARDITIS DURING PREGNANCY

Table 1
A proposed treatment scheme for medical therapy of pericarditis during pregnancy.

Drug	Pregnancy		After delivery
	<20 weeks	>20 week	During breastfeeding
Aspirin[a] 250 to 750 mg every 8 h	Allowed	To be avoided	Preferably avoided
NSAIDs (ibuprofen, indomethacin, naproxen)	Allowed	To be avoided	Allowed
Paracetamol	Allowed	Allowed	Allowed
Prednisone 2,5 to 10 mg daily, at the lowest effective dose	Allowed[b]	Allowed[b]	Allowed[b]
Colchicine	Allowed	Allowed	Allowed

Pregnancy should be planned in a phase of disease quiescence and followed by multidisciplinary teams with experience in the field. During pregnancy tapering of therapy should be extremely cautious. Normal vaginal delivery is possible and should be considered in absence of contraindications.
During pregnancy and breast feeding anti-histamine H2 blockers or proton pump inhibitors (PPI) may be used.
Supplementation with calcium and vitamin D (1500 mg/day and 800 IU/day, respectively) should be offered to all women taking corticosteroids in pregnancy and lactation.
[a] Low-dose aspirin is not expected to have substantial anti-inflammatory activity but may reduce the risk of preeclampsia in women at risk [22].
[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

https://doi.org/10.1016/j.ijcard.2019.02.003

PERICARDITIS AND PERICARDIAL EFFUSIONS IN END-STAGE RENAL DISEASE

TABLE 1. Presentation of pericarditis in the ESRD population

Pleuritic chest pain sometimes positional
Friction rub
Fevers/chills
Dyspnea
Cough
Malaise
Hypotension during dialysis
Signs and symptoms of heart failure

DOI: 10.1111/sdi.12517

CLASSIFICATION

- In our current classification, uremic pericarditis is defined as pericarditis that develops before or within 8 weeks of initiation of dialysis, while dialysis-associated pericarditis is used to define pericarditis in patients on dialysis for more than 8 weeks .
- Constrictive pericarditis is thought to represent the end stage of inflammation, of any etiology, of the pericardium and remains a rare complication in ESRD patients.
- Pericarditis in dialysis patients appeared to be less responsive to solute clearance with dialysis or intensification of dialysis, was more symptomatic, was more likely to have sanguineous or hemorrhagic pericardial fluid, and was more frequently associated with tamponade and hemodynamic instability.

DOI: 10.1111/sdi.12517

MANAGEMENT

- Uremic Pericarditis
  - Initiation of Dialysis
  - Development of uremic pericarditis is an absolute indication for initiation of RRT and ESC guidelines from 2004 recommend use of heparin-free HD . Since uremic pericarditis responds well to initiation of RRT alone, other measures are rarely indicated.
- Dialysis-associated Pericarditis
  - Intensification of Dialysis
  - Switching to PD/Intensification of PD
- Medical therapy role:
  - colchicine has not been studied in uremic or dialysis-associated pericarditis perhaps due to the higher risk of toxicity in this population, especially if the dose is not significantly reduced.
  - The literature on treating uremic or dialysis-associated pericarditis with steroids is minimal with studies being very small and with generally poor outcomes.
- Surgical treatments for recurrent pericardial effusions
  - Repeat needle pericardiocentesis
  - Pericardiostomy with continuous catheter drainage (with or without intrapericardial steroids)
  - Pericardial window/partial pericardiectomy
  - Complete pericardiectomy

DOI: 10.1111/sdi.12517

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PERICARDITIS IN PATIENTS WITH CORONAVIRUS DISEASE 2019

- A total of 33 studies (32 case reports and 1 case series) involving 34 patients were included. The mean age was 51.6 ± 19.5 years and 62% of patients were men. Sixty-two percentage of patients were diagnosed with myopericarditis. The most frequent electrocardiographic pattern (56%) was diffuse ST-elevation and PR depression. Pericardial effusion and cardiac tamponade were reported in 76 and 35% of cases, respectively. The median values of C-reactive protein [77 mg/dl (12-177)] and white blood cells [12 335 cells/μl (5625-16 500)] were above the normal range. Thirty-eight percent and 53% of patients were treated with nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine, respectively. These drugs were more frequently used in patients with acute pericarditis compared with myopericarditis. The in-hospital mortality was 6% without a significant difference between both groups.
- **Conclusion:** Our review shows that COVID-19 patients with pericarditis had similar clinical features to other viral cardiotropic infections. However, NSAIDs and colchicine were used in half or less of the cases. Overall, the short-term prognosis was good across groups.

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