Idiopathic Recurrent Pericarditis

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Abstract

Idiopathic recurrent pericarditis (IRP) is a subset of pericarditis characterized by frequent true recurrences (free interval between two flares longer than 4 weeks). The term "idiopathic" refers to a non-specific etiology and is used even if an autoinflammatory pathway is suspected. The diagnosis is based on the association of typical symptoms and signs (mainly pericardial chest pain plus pericardial rub or electrocardiographic alterations or pericardial effusion). The monitoring of inflammatory markers and the use of imaging techniques help to guide management. Standard treatment includes the combination of non-steroidal anti-inflammatory drugs (NSAIDs) plus colchicine. In cases that do not respond to this combination, therapy with interleukin-1 inhibition has been remarkably effective.

Keywords

Pericarditis · Recurrent pericarditis
Autoimmune diseases · Autoinflammatory diseases · Colchicine · Immunotherapy
Anakinra · Echocardiography
Cardiac magnetic resonance

Abbreviations

AHA	Anti-heart antibodies
AIDA	Anti-intercalated-disk antibodies
AIRTRIP	The Anakinra-Treatment of Recurrent Idiopathic Pericarditis
ANA	Anti-nuclear antibodies
AP-1	Activator protein-1
APC	Antigen-presenting cell
ASA	Acetylsalicylic acid
CEACAM1	Carcinoembryonic antigen cell adhesion molecule 1
CMR	Cardiac magnetic resonance
CMV	Cytomegalovirus
CRP	C-reactive protein
CT	Computerized tomographic
DAMP	Damage-associated molecular patterns
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ESC	European Society of Cardiology

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ESR	Erythrocyte sedimentation rate
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigens
HSV-1	Herpes simplex virus
IL	Interleukin
INF	Interferon γ
IRP	Idiopathic recurrent pericarditis
IVIg	Intravenous immunoglobulins
MHC	Major histocompatibility complex
MICA	MHC class I chain related protein A
NF-kB	Nuclear factor-kappa B
NSAIDs	Nonsteroidal anti-inflammatory drugs
PAMP	Pathogen-associated molecular patterns
PPS	Postpericardiotomy syndrome
STIR	Short-tau inverted recovery
TLR	Toll-like receptor
TNF	Tumor necrosis factor
TRAPS	TNF receptor-associated periodic fever syndrome

Key Points

- **Idiopathic recurrent pericarditis may often have an autoinflammatory pathogenesis**
- **Idiopathic recurrent pericarditis is a diagnosis of exclusion (approach guided by pre-test probability that a specific condition is present)**
- **Inflammatory markers and imaging can support the diagnosis and management**
- **Interleukin-1 antagonists are very effective in difficult-to-treat patients**

36.1 Introduction

Pericarditis is a clinical disorder in which similar clinical pictures may be sustained by different mechanisms. The spectrum of possible causes is broad and the mechanisms not completely understood; in about 70% of pediatric patients and more than 80% of adult patients a specific etiology cannot be detected and pericarditis is therefore considered idiopathic [1, 2], even if the etiopathogenesis is presumed to be viral or immune-mediated. Typically the disease has a good prognosis with a full recovery within several weeks. However in about 20–40% of cases relapses occur. Recurrences are one of the most challenging management issues and a common reason of concern for both the physician and the patient. In recent years idiopathic recurrent pericarditis (IRP) has been considered to be autoinflammatory in its behavior. The dramatic beneficial effect of the interleukin (IL)-1 receptor antagonist anakinra has solidified this notion and led to the consideration of a new pathogenetic scheme [3, 4].

36.2 Definition/Classification

The recent European Society of Cardiology (ESC) guidelines have defined acute pericarditis as an inflammatory pericardial syndrome with specific manifestations, including chest pain (85–90% of cases), usually sharp, improved by sitting up and leaning forward, the presence of a pericardial friction rub (≤1/3 of cases), electrocardiogram (ECG) changes (up to 60% of cases)—with new widespread ST elevation or PR depression in the acute phase, and pericardial effusion (up to 60% of cases) assessed by echocardiography [2]. Supportive findings include elevation of inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and the white blood cell count or other imaging evidence of pericardial inflammation [2].

Recurrent pericarditis is defined as a relapse of disease after a documented first acute episode followed by a symptom-free interval of at least 4 weeks or longer, corresponding to the completion and usual duration of anti-inflammatory therapy in most non-complicated cases [2]. It is suggested to differentiate recurrent pericarditis from *incessant* pericarditis, in which symptoms persist for more than 4–6 weeks but less than 3 months, and from *chronic* pericarditis, in which the symptoms last longer than 3 months [2].

36.3 Epidemiology

There are limited data documenting the precise incidence of idiopathic recurrent pericarditis. Acute pericarditis is common. An Italian registry reported an incidence as 27.7 cases per 100,000 population per year [2] but a recent study from Denmark documented a higher incidence (almost 168 cases per 100,000 population per year) [5]. The Italian study addressed only data from emergency rooms and hospital admissions, and the diagnosis of acute pericarditis was confirmed by the investigators, while the Danish study included also outpatients visits and probably also pericardial effusions from other causes; this may explain the apparent discrepancy between the two studies. The frequency of recurrences varied in different studies between 20 and 30% after the first episode and between 20 and 50% after the first relapse [2]. Higher frequencies are generally related to an inadequate treatment of the previous attack. A positive family history has been described in 10% of patients with recurrent idiopathic pericarditis [6].

36.4 Etiology

The causes of pericarditis are numerous and heterogeneous. Multiple triggers can initiate or precipitate the inflammatory reaction. Causes can be divided into two major categories: infectious (any type of microorganisms) and non-infectious (autoimmune, neoplastic, metabolic, traumatic or iatrogenic, drug-related and miscellaneous) [2]. In approximately 70% of pediatric patients and more than 80% of adults a specific etiology cannot be detected and pericarditis is therefore considered idiopathic.

36.5 Pathogenesis

- **Many non-specific stimuli (including viruses) may trigger attacks of acute pericarditis**
- **An autoinflammatory pathway with inflammasome activation and IL-1 release has a pivotal role in many patients**

The pathogenesis of recurrent pericarditis is currently unknown. Infectious (mainly viral), autoimmune or autoinflammatory mechanisms have been proposed.

An infectious hypothesis is supported by molecular analysis on pericardial fluid and epicardial biopsies that identified a virus in almost 20% of cases [1]. However, standard laboratory techniques are not diagnostic in the majority of cases. Recurrent attacks may result from an inability to clear a presumed viral infection. This could explain the increased risk of relapse in patients treated with corticosteroids. Anti-viral therapy is generally not considered.

Some laboratory findings seem to confirm an autoimmune pathway: antinuclear antibodies (ANA) [7] are found in about 40% of patients with recurrences as well as anti-heart and anti-intercalated-disk autoantibodies, in 50 and 25% of patients with IRP, respectively [8]. Other findings suggestive of an autoimmune pathway include the detection of proinflammatory cytokines, such as IL-6, IL-8 and interferon (INF)-γ in pericardial fluid, and the association of IRP with human leukocyte antigen (HLA)-A*02, HLA-Cw*07, and HLA-DQB1*0202, and in a lower frequency HLA-DQB1*0302 [9]. In addition, recurrent pericarditis is not an infrequent manifestation of systemic autoimmune disease, usually during a flare. It can occur in the context of systemic lupus erythematosus (20–50% of patients), vasculitides, rheumatoid arthritis and Sjogren syndrome [1, 9]. Post cardiac injury syndrome may be considered a model of autoimmune pericarditis. This syndrome is triggered by damage to pericardial tissue or the presence of blood in the pericardial cavity, related to open heart surgery and other minor procedures or during myocardial ischemia. The exposure of pericardial antigens may result in an autoimmune response activating T- and B lymphocytes. However, the role of autoantibodies in the process is not clear, as they may only be a consequence of the antigenic exposure rather than a cause of the inflammatory process [10]. While ANA may be detected, these are generally at low titres (1/40 to 1/80), are not disease-specific and

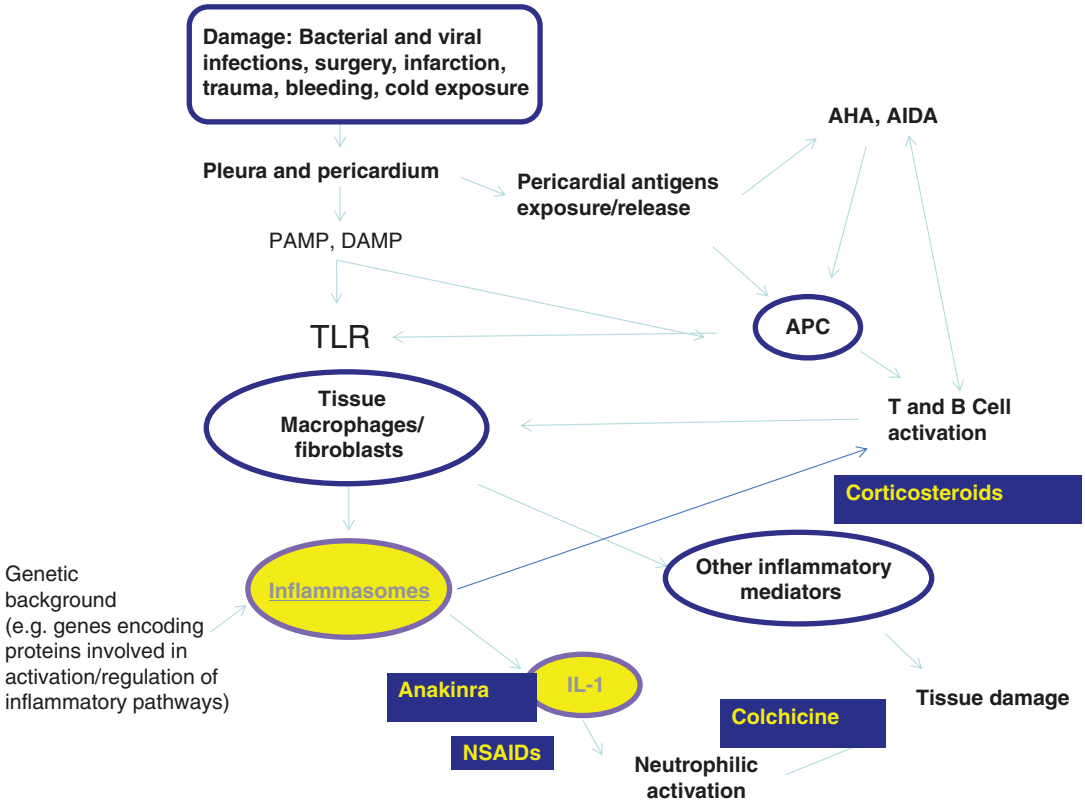

Fig. 36.1 The interplay among etiological agents, genetic factors and the immune system as determining the course of pericarditis and relapses. Drugs interfere with the release of inflammatory cytokines, acting in different steps of inflammatory cascade. *PAMP* pathogen-associated molecular patterns; *DAMP* damage-associated molecular patterns; *TLR* toll-like receptor; *AHA* anti-heart antibodies; *AIDA* anti-intercalated-disk antibodies; *IL-1* interleukin-1; *NSAIDs* nonsteroidal anti-inflammatory drugs; *APC* antigen-presenting cell

have limited clinical significance [11], as they are equally distributed in patients with IRP with or without rheumatologic disorders.

The third hypothesis proposes the involvement of the innate immune response. It derives from the recent demonstration of the spectacular efficacy of the IL-1 receptor antagonist anakinra in the treatment of recurrent pericarditis [3, 4, 12]. Recurrent episodes of pericarditis can be observed in several monogenic autoinflammatory diseases such as familial Mediterranean fever, mevalonate kinase deficiency and tumor necrosis factor (TNF) receptor-associated periodic fever syndrome (TRAPS) [13]; we observed that 6% of IRP patients carried a mutation in the *TNFRSF1A* gene (often the non-specific R92Q mutation) [14]. The dramatic effect of IL-1 inhibition suggests an important role for the inflammasome in the pathogenesis of the disease [15].

In summary, it appears that while the initial eliciting causes of pericarditis may differ the mechanisms that sustain at least the recurrence of the disease are autoinflammatory in nature, with a leading role for IL-1 (Fig. 36.1).

36.6 Clinical Manifestations

The main symptom of recurrent pericarditis is anterior chest pain, worsened by lying supine and improved by leaning forward and described by the patient as similar to previous attacks. Also, at least one objective finding of pericarditis (pericardial rub, ECG changes, and pericardial effusions) may be present [2]. These symptoms are often attenuated during recurrences, mainly during treatment. In the subset of patients with more aggressive manifestations, fever, involvement of other serosal

Table 36.1 Comparison of clinical features, etiologies and outcomes in pediatric patients (Finetti, Raatikka, Imazio) and adults (CORP2) with recurrent pericarditis according to largest published studies

Feature	Raatikka [18]	Finetti [3]	Imazio [17]	CORP 2 [19]
Number of patients studied	15	15	110	240
Fever	12 (80%)	8 (53%)	84 (76%)	73 (30%)
Chest pain	15 (100%)	13 (87%)	103 (93.6%)	239 (100%)
Pericardial rub	n/a	5 (33%)	31 (28%)	82 (34%)
ECG	10/13 (77%)	13 (87%)	49 (44%)	25% [24]
Pericardial effusion	15 (100%)	13 (87%)	86 (78%)	138 (57%)
Elevated CRP	14 (93%)	13 (87%)	102 (93%)	174 (72%)
Tamponade	1 (7%)	n/a	15 (14%)	2 (1%)
No specific etiology	8 (53%)	13 (87%)	98 (89%)	198 (82%)
PPS	7 (47%)	n/a	10 (9%)	21 (9%)
ANA positivity	1(N = 14) (7%)	n/a	18 (16%)	43% [7]
ASA/NSAIDs	4 (27%)	13 (87%)	89 (81%)	240 (100%)
Colchicine	4 (27%)	14 (93%)	68 (62%)	120 (50%)
Corticosteroids	11 (73%)	15 (100%)	70 (65%)	16 (7%)
Anakinra	0	13 (87%)	12 (17.1%)	0
Constriction (transient)	0 (0.0%)	n/a	3 (3%)	4 (7%)
Pleuropulmonary involvement	10 (67%)	n/a	54%	36% [16]
Liver involvement	n/a	n/a	9 (8%)	8% [16]

ECG electrocardiogram; *CRP* C-reactive protein; *PPS* postpericardiotomy syndrome; *ANA* anti-nuclear antibodies; *ASA* acetylsalicylic acid; *NSAIDs* nonsteroidal anti-inflammatory drugs, *n/a* not applicable

membranes (pleuropulmonary involvement in 36% of adults and 55% of children, peritoneal involvement in 5%) and elevation of liver enzymes (8% in adult) can be present [16].

In the pediatric age group the clinical presentation is often more acute and inflammatory, with more frequent pleuropulmonary and systemic involvement. However, ANA are present less frequently in children. Overall, the autoinflammatory pattern is often more evident in children with high fever, strikingly elevated CRP and pleuropulmonary involvement [3, 17] (Table 36.1).

36.7 Laboratory Testing

No specific laboratory marker is diagnostic for pericarditis. The ESC has proposed a general diagnostic approach to acute pericarditis, defining the first level investigations [2]. These include complete blood count, markers of inflammation, renal and liver function tests, thyroid function, markers of myocardial involvement (i.e. troponin, serum level of creatine kinase), ECG, echocardiography, chest radiograph and limited additional tests in related to the suspected etiology and clinical presentation [2]. The specific clinical manifestations in an individual patient should guide the diagnostic approach. Additional testing should be related to the suspected origin and clinical presentation (low-risk vs high risk; hospitalization vs non-hospitalization), based on the pre-test probability that a specific condition is present, according to the ESC guidelines [2]. In cases of recurrence three specific causes must be excluded: tuberculosis, malignancy and systemic autoimmune disease. Viral serological tests are considered futile, since viral identification has no impact on therapy and prognosis. A possible exceptions are those for human immunodeficiency virus (HIV) and hepatitis C virus (HCV). If a viral etiology is strongly suspected, generally in the first attack, a genome search with PCR is now preferred for most viruses to serology, including parvovirus, herpes simplex virus-1 and -2 (HSV 1 and 2), cytomegalovirus (CMV), Epstein-Barr virus (EBV), adenovirus and enteroviruses (echo and coxsackie viruses) [2].

In case of a positive family history for pericarditis or autoinflammatory (periodic fever) syndromes genetic tests for monogenic syndromes are indicated [13, 14].

CRP and ESR and other parameters of inflammation, even if not specific, are important to help

define the intensity of the inflammatory process [20]. A small study reported the use of the carcinoembryonic antigen cell adhesion molecule 1 (CEACAM1) and the major histocompatibility complex (MHC) class I chain related protein A (MICA) as biomarkers, but further investigations are needed to clarify their possible application [21].

36.8 Imaging

Transthoracic echocardiography is the preferred imaging modality for the diagnosis of pericarditis [2]. It is a simple, non-invasive and low-cost imaging technique that can be easily performed at the bedside and in urgent/emergency settings. Furthermore it is safe and can be repeated many times without health risks. It supports the diagnosis by identifying a pericardial effusion and can show complications such as tamponade, constriction, ventricular dysfunction, etc. (Fig. 36.2). However, echocardiography does not provide precise information regarding the inflammatory process. In fact, reports of increased thickness or hyperechogenicity of the pericardium are not specific and are often limited by artefacts.

Cardiac magnetic resonance (CMR) (Fig. 36.3) is a second-level imaging technique and is helpful to study pericardial and myocar-

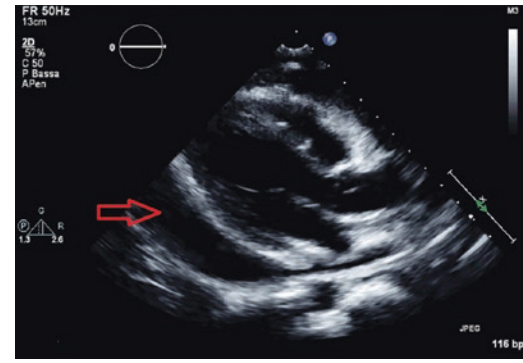

Fig. 36.2 Echocardiographic findings in acute pericarditis. The red arrow indicates a large circumferential pericardial effusion

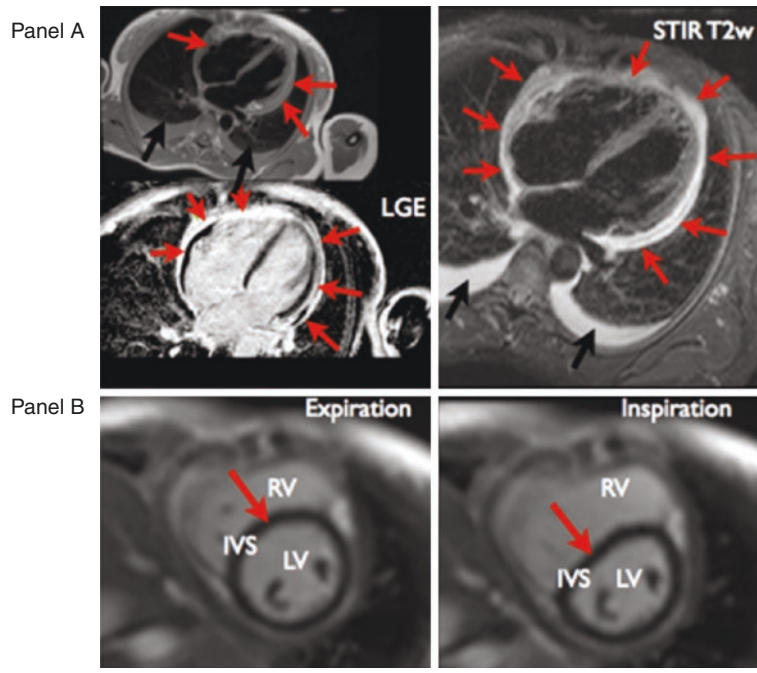

Fig. 36.3 Pericardial thickening with pericardial inflammation on CMR study (see red arrows in panel (**A**), pericardial edema on STIR T2w image and pericardial late gadolinium enhancement, concomitant pleural effusion is marked with black arrows). On panel (**B**) septal bounce is seen (see red arrows) due to exaggerated interventricular interdependence by real-time CMR imaging, expression of transient pericardial constriction. *CMR* cardiac magnetic resonance; *STIR* short-tau inverted recovery; *LGE* late gadolinium enhancement; *RV* right ventricle; *IVS* interventricular septum; *LV* left ventricle

dial tissues [2, 22]. On T1-weighted imaging the normal pericardium appears like a thin hypointense ("dark") curvilinear structure surrounded by hyper-intense ("bright") mediastinal and epicardial fat. CMR can assess pericardial thickness (normal value is <4 mm) and pericardial edema. On T2-weighted short-tau inverted recovery (STIR) fast spin-echo sequences, pericardial edema appears bright. The tissue edema is not well defined if there is a concomitant effusion, which appears as bright as the edema. Following intravenous administration of paramagnetic gadolinium chelates, enhancement may show extension of inflammation into the surrounding epicardial fat, which suggests severe inflammation. CMR is useful also in showing myocardial inflammatory involvement, fibrosis and evolving constrictive pericarditis. The technique has some disadvantages, first of all its limited availability and its costs and also the need of breath-holding and regular heart rhythms to get a better picture quality. Contraindications include pacemakers, claustrophobia and renal insufficiency.

Computerized tomographic (CT) scanning is considered a complementary imaging modality (Fig. 36.4). It is useful in order to assess anatomic features and presence of calcifications [2,

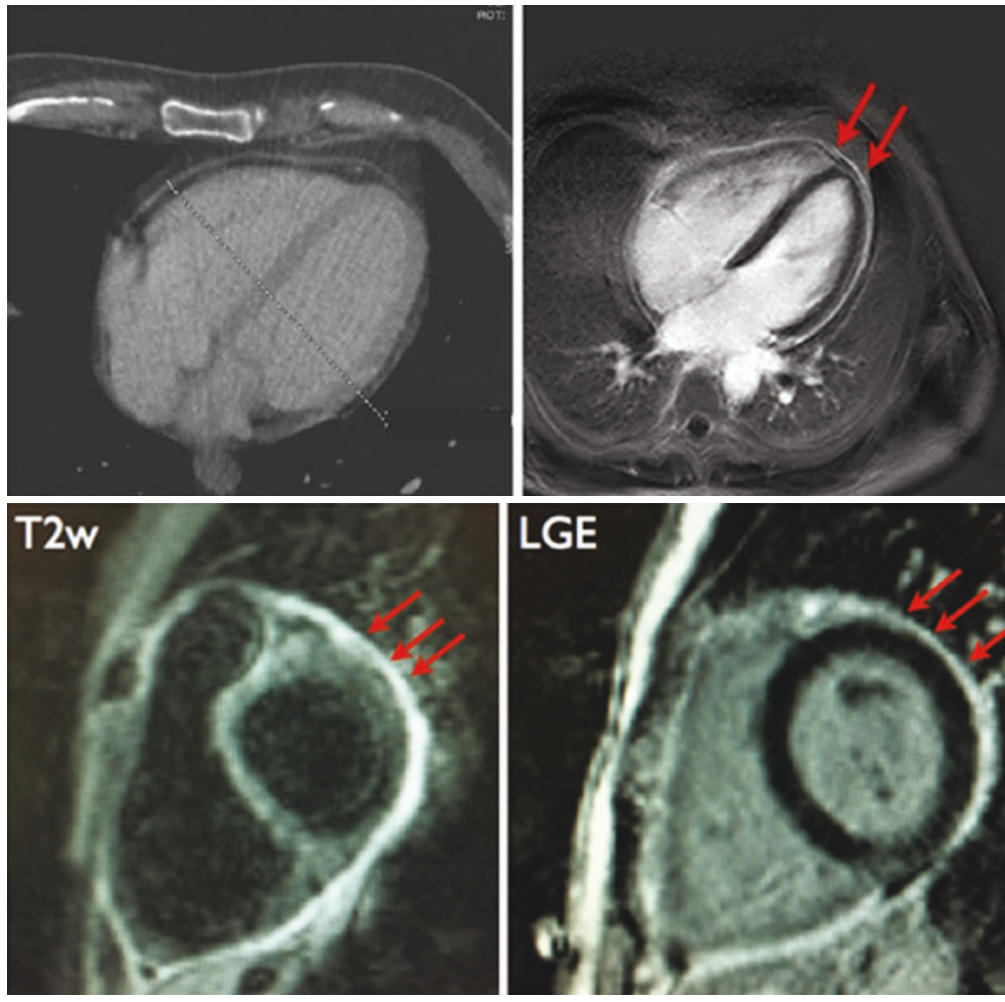

Fig. 36.4 Pericardial inflammation is detected by mild contrast-enhancement of the pericardium by CT (TAC). Pericardial edema is particularly evident by cardiac magnetic resonance on STIR T2w image and as pericardial late gadolinium enhancement (see red arrows)

23]. On CT, the normal pericardium is visible as a thin curvilinear structure surrounded by the hypodense mediastinal and epicardial fat, and has a thickness ranging from 0.7 to 2.0 mm. CT can depict focal effusions, precisely quantify the amount of fluid and, depending on attenuation values of fluid (HU), it can provide information about the nature of the effusion. Low attenuation values (e.g. 0–20 HU) suggest a transudate, intermediate values (e.g. 20–60 HU) are indicative of exudative effusions, while high attenuation values (>60 HU) suggest haemorrhage. Intravenous administration of iodinated contrast material may allow the detection of pericardial inflammation because of the enhancement of the inflamed pericardium after contrast injection. CT is the first choice in the pre-operative work-up in case of pericardiectomy, in order to appraise the extension of calcification of the pericardium. It is also useful to exclude specific causes, mainly neoplastic disease, if extended to the remainder of the chest and abdomen [23]. Its limits are mainly related to radiation exposure and renal insufficiency, if iodine contrast is used.

36.9 Treatment

- **The therapy of pericarditis is based on the association between high-dose non-steroidal anti-inflammatory drugs, low-dose colchicine and eventually also corticosteroids at low doses**
- **Immunotherapy should be considered in case of treatment-resistant cases. These include azathioprine, intravenous immunoglobulins and interleukin-1 antagonists**
- **IL-1 antagonists (anakinra) are very effective in difficult-to-treat patients**

In the past the treatment of pericarditis was largely empirical, because its etiology and mechanisms were usually unknown. Better understanding of the inflammatory basis of pericarditis has led to more rational use of treatment and a novel therapeutic approach.

The cornerstone of therapy for pericarditis remains anti-inflammatory therapy with either aspirin or non-steroidal-anti-inflammatory drugs (NSAID) plus colchicine [2]. NSAIDs must be taken at high anti-inflammatory doses (Tables 36.2 and 36.3).

Table 36.2 Aspirin and non-steroidal anti-inflammatory drugs in the treatment of pericarditis: recommended regimens in adults (modified from guidelines). The wide dosages ranges are based on weight, age, severity of the attack and subjective tolerability

Drug	Treatment dose	Length of treatment	Tapering
Aspirin	500–1000 mg every 6–8 h (1.5–4 g/d)	FIRST attack: 2–4 weeks RECURRENCES: several weeks to 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. Gradual tapering (every 1–2 weeks and only if the patient is asymptomatic and CRP is normal), is recommended	Decrease the total daily dose by 250–500 mg every 2–4 weeks
Ibuprofen	600–800 mg every 8 h (1600–3200 mg daily)		Decrease the total daily dose by 200–400 mg every 2–4 weeks
Indomethacin	25–50 mg every 8 h (150 mg daily)		Decrease the total daily dose by 25 mg every 2–4 weeks
Naproxen	250–500 mg every 12 h; maximal daily dose 1500 mg 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

Start at the lower end of dosing range and titrate upward. According to local availability of the different agents we recommend intravenous use of NSAIDs in hospitalized symptomatic patients
Geriatric dosing: refer to adult dosing. Use lowest recommended dose and frequency
Renal impairment dosing: CrCl <30 mL/min: NSAIDs use is not recommended (for aspirin: use is not recommended if CrCl <10 mL/min)
Hepatic impairment dosing: use with caution; dose adjustment may be required [2]
CRP C-reactive protein; *NSAIDs* nonsteroidal anti-inflammatory drugs

Table 36.3 Aspirin and non-steroidal anti-inflammatory drugs: recommended doses in children with pericarditis (modified from guidelines)

Drug	Treatment dose	Length of treatment and tapering
Ibuprofen	30–50 mg/kg/24 h divided every 8 h; maximum: 2.4 g/day	FIRST attack: 2–4 weeks. RECURRENCES: several weeks to months The optimal length of treatment is debatable, and CRP should probably be as a marker of disease activity to guide management and treatment length. A gradual tapering (every 2–4 weeks and only if the patient is asymptomatic and CRP is normal), should be considered
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 20 mg/kg/day has been tolerated)	

Start at the lower end of dosing range and titrate upward. *CRP* C-reactive protein

Colchicine is recommended without a loading dose and using weight-adjusted doses (i.e. 0.5 mg once daily if body weight is<70 kg or 0.5 mg twice daily if it is ≥70 kg, for ≥6 months) in adults, in order to improve remission rates and prevent recurrences [2, 24]. In children with IRP commonly used doses are 0.5 mg/day in children younger than 5 years and 1–1.5 mg/day in older children [2]. Higher doses, sometimes used in familial Mediterranean fever, have generally not been considered (see Chap. 41 for further details on the mechanism and use of colchicine).

In cases of incomplete response corticosteroids may be added particularly in adults to aspirin/NSAIDs and colchicine as a triple therapy, but at low to moderate doses (i.e. prednisone 0.2–0.5 mg/kg/day in adults) [2].

Corticosteroids block transcription factors such as nuclear factor-kappa B (NF-kB) and activator protein-1 (AP-1) which are involved in the transcription of several inflammatory mediators.

Although corticosteroids provide rapid relief of symptoms, they increase the risk of the pericarditis turning into chronic disease or increased number of recurrences [2, 16, 17, 19, 22, 24], and have many side effects. They should be used only in selected patients with specific indications (i.e. systemic inflammatory diseases, post-pericardiotomy syndromes, impending cardiac tamponade, pregnancy), NSAID contraindications (true allergy, high risk of bleeding, renal insufficiency), and intolerance or resistance to standard therapy [2]. If corticosteroids are used, they should be tapered very slowly. Therapy and subsequent tapering should be guided by CRP values as an indicator of the inflammatory process and the potential for relapse. Long-term corticosteroid use is particularly worrisome in pediatric patients due to their multiple side-effects, including growth impairment.

36.9.1 Immunotherapy and IL–1 Inhibition

Immunotherapy is an alternative approach to the treatment of resistant IRP [2]. Three medications have been proposed: azathioprine, intravenous immunoglobulin (IVIg) and anakinra.

Data of the efficacy of azathioprine as therapy for IRP are few and based only on case reports or case series of adults and one retrospective cohort study [25].

The use of IVIg was reported in two small case series and one retrospective analysis describing only 14 cases [2]. IVIg has a rapid onset of action and can be used as a corticosteroid-sparing agent. However, the high cost and lack of good evidence do not really support its routine administration.

Anakinra is a recombinant IL-1 receptor antagonist that inhibits the action of IL-1 (see Chap. 42). The IL-1 intracellular signaling pathway is involved in the activation of T cells, stimulation of metalloproteinases, prostaglandin release by macrophages and in chemotaxis of monocytes, lymphocytes and polymorphonuclear leukocytes. Anakinra was initially developed for

the treatment of rheumatoid arthritis but has found its niche in the treatment of many autoinflammatory diseases. Its efficacy in IRP was first recognized in the pediatric population [3, 17], and this proof of concept was of paramount importance. Data derived from case reports, cohort studies, one retrospective analysis and a meta-analysis, confirmed these findings. A recent double-blind randomized controlled trial (AIRTRIP-The Anakinra-Treatment of Recurrent Idiopathic Pericarditis) formally demonstrated the spectacular effects of anakinra in 21 patients with corticosteroid-dependent and colchicine-resistant recurrent pericarditis with elevated CRP [4]. Anakinra proved highly effective, achieving quick symptoms relief in a few days and allowed steroid discontinuation in all patients within 6 weeks. It is administered as a once daily subcutaneous injection at 1–2 mg/kg/d (maximal 100 mg) for several months [4]. After clinical stabilization recurrences can occur if tapering is too rapid. Tapering regimes are not well established yet. A possible scheme might be to withdraw a dose every month after a full control of the disease has been reached: e.g. 1st step 100 mg/d, every day for 6 months; 2nd step in the 7th month, 100 mg/d, 6 times per week; 3rd step 100 mg/d, 5 times per week for 1 month, and so on until the 7th step, 100 mg once per week, in the 14th month. A critical point for recurrence might be at the dose of 2 doses weekly.

The drug is generally well tolerated. The most common adverse events are skin reactions at the site of injection, neutropenia and mild elevation of transaminases.

In children anakinra might now be considered prior to corticosteroids, to avoid their side-effects in the growing child. There are only few case reports on the use of other anti-IL1 antagonists in IRP.

36.10 Outcome/Prognosis

Severe complications are uncommon in IRP [2]. Cardiac tamponade is rare and generally occurs at the beginning of the disease. Constrictive pericarditis has not been reported in IRP, despite numerous recurrences [16, 26], and the overall risk is lower than that recorded after a first episode of acute pericarditis (less than 1%) [27]. Thus, it is important to reassure patients about their prognosis, explaining the nature of the disease and its likely course. Drug treatment should take into account this favourable outcome to avoid more toxic agents. However, the quality of life can be severely impaired in patients with repeated recurrences and corticosteroid dependence [2]. IRP may last for years with recurrent flares if not properly treated. IL-1-inhibitors have proved to be rapidly acting and highly efficient also in refractory cases and their role in the management of IRP is becoming more prominent. In our experience most patients continue treatment for 1–3 years, at low doses. At present, approximately 40% have discontinued treatment. In case of recurrence during anakinra tapering, NSAIDs may be useful to control mild recurrences [4].

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