Recurrent Pericarditis

7

Antonio Brucato, Anna Valenti, and Silvia Maestroni

Abbreviations

AHA	Anti-heart antibodies
AIDA	Anti-intercalated-disk antibodies
AIRTRIP	The Anakinra-Treatment of Recurrent Idiopathic Pericarditis
ANAs	Antinuclear 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 tomography
DAMP	Damage-associated molecular patterns
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ESC	European Society of Cardiology
ESR	Erythrocyte sedimentation rate
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigens
HSV-1	Herpes simplex virus

A. Brucato
Dipartimento di Scienze Biomediche e Cliniche Università degli Studi di Milano, Ospedale Fatebenefratelli, Milano, Italy
e-mail: antonio.brucato@asst-fbf-sacco.it

A. Valenti · S. Maestroni (✉)
Medicina Interna Ospedale Papa Giovanni XXIII, Bergamo, Italy
e-mail: avalenti@asst-pg23.it; smaestroni@asst-pg23.it

R. Cimaz (ed.), *Periodic and Non-Periodic Fevers*, Rare Diseases of the Immune System,
https://doi.org/10.1007/978-3-030-19055-2_7

IL	Interleukin
INF	Interferonγ
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

Chapter Overview

- Idiopathic recurrent pericarditis may have an autoinflammatory pathogenesis.
- Idiopathic recurrent pericarditis is a diagnosis of exclusion.
- Inflammatory markers and imaging can support the diagnosis and management.
- Interleukin-1 antagonists are effective in difficult-to-treat patients.

Pericarditis is an entity characterized by similar clinical pictures sustained by different pathways. The spectrum of possible causes is broad: in about 70% of children and more than 80% of adults, a specific etiology cannot be detected, and pericarditis is therefore labeled idiopathic [1, 2], even if the etiopathogenesis is suspected to be viral- or immune-mediated. Idiopathic forms typically have a good prognosis with often a full recovery within several weeks. However, pericarditis may recur in about 20–40% of the cases, and recurrences are the most challenging common management issue and a frequent reason of concern for both the physician and the patient. Recently, idiopathic recurrent pericarditis (IRP) has been considered to be sustained by an autoinflammatory pathway. The spectacular effect of the interleukin (IL)-1 receptor antagonist anakinra has reinforced this notion and has led to the consideration of a new pathogenetic mechanism [3, 4].

7.1 Definitions

The European Society of Cardiology (ESC) guidelines define acute pericarditis as an inflammatory pericardial syndrome with specific manifestations, including chest pain (85–90% of cases), typically sharp, improved by sitting up and leaning forward; pericardial friction rub (30% of cases); electrocardiogram (ECG) changes (60% of cases)—with new widespread ST elevation or PR depression or nonspecific repolarization abnormalities; and pericardial effusion (60% of cases in the first attack and

50% in the recurrences) assessed by echocardiography [2]. Confirmatory findings include elevation of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and the white blood cell count or evidence of pericardial inflammation with computerized tomographic (CT) scan or cardiac magnetic resonance (CMR) [2]. Recurrent pericarditis is defined as a relapse after a first acute episode followed by a symptom-free interval of at least 4 weeks, corresponding to the usual duration of anti-inflammatory therapy in noncomplicated cases [2]. Recurrent pericarditis Recurrent pericarditis

may be differentiated 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].

7.2 Epidemiology

Limited data describe the incidence of IRP. Acute pericarditis is common. The incidence was 27.7 cases per 100,000 population per year in an Italian community [2], but a study from Denmark reported a higher incidence (168 cases per 100,000 population per year) [5]. The Italian paper evaluated only data from emergency rooms and hospital admissions, and the diagnosis was confirmed by the investigators, while the Danish study included also outpatients and pericardial effusions not due to acute pericarditis; this probably explains the observed discrepancy between the two studies. The rate of recurrences varied in studies between 20% and 30% after the first episode and between 20% and 50% after the first recurrence [2]. Recurrences may be related to an inadequate treatment of the previous attack. Familiarity has been reported in 10% of the patients with IRP [6].

7.3 Etiology

The etiology of pericarditis is heterogeneous. Several nonspecific triggers may activate the inflammatory cascade. Two major categories are recognized: infectious (viruses, mycobacteria, other bacteria) and noninfectious (neoplastic, autoimmune, traumatic, metabolic, iatrogenic, drug-related) [2]. In 70% of pediatric patients and more than 80% of adult patients, a definite etiology cannot be recognized, and pericarditis is therefore labeled idiopathic.

7.4 Pathogenesis

The pathogenesis of IRP is not known. Infectious (mainly viral), autoimmune, or autoinflammatory pathways have been suggested.

An infectious mechanism is proposed by molecular analysis on epicardial biopsies and pericardial fluid that identified a virus in approximately 20% of cases [1]. However, standard techniques are not diagnostic in the vast majority of cases. Recurrences may theoretically result from inability to clear the virus. This might explain the increased risk of relapse in patients treated with corticosteroids, even if

too rapid, corticosteroid tapering is often the more probable cause of most of these cases. Overall, antiviral therapy is usually not considered.

Some observations suggest an autoimmune pathogenesis: antinuclear antibodies (ANAs) [7] are present in about 40% of the patients with IRP as well as anti-heart and anti-intercalated-disk antibodies, in 50% and 25% of IRP patients, respectively [8]. Other supportive observations for an autoimmune mechanism include the presence of cytokines, such as interferon (INF)-γ, IL-8, and IL-6, in the pericardial fluid, and the association of IRP with human leukocyte antigen (HLA) DQB1∗0202A∗02, Cw∗07, and in a lower frequency DQB1∗0302 [9]. Moreover, pericarditis is common in systemic autoimmune disease, such as systemic lupus erythematosus (20–50% of patients), systemic sclerosis, rheumatoid arthritis, and Sjögren's syndrome, usually during a flare [1, 9]. Post-cardiac injury syndrome is sometimes considered a model of autoimmune pericarditis, triggered by damage to pericardium or blood in the pericardial space, due to open heart surgery or other invasive procedures or after myocardial infarction. The exposure of pericardial antigens may induce an autoimmune response activating B- and T lymphocytes [10]. On the other hand, an autoinflammatory pathogenesis may also be involved (production of massive amount of damage-associated molecular patterns [DAMP]).

ANAs may be positive in patients with IRP, even if generally at low titers (≤1/80); they are not specific and have low clinical significance [11], since they are equally positive in patients with recurrent pericarditis associated or not with a definite rheumatologic disease.

The last and more recent hypothesis suggests the involvement of the innate immune system. The demonstration of the spectacular effect of anakinra in refractory recurrent pericarditis was a sort of proof of concept [3, 4, 12]. Pericarditis may be observed in many monogenic autoinflammatory diseases such as familial Mediterranean fever, tumor necrosis factor (TNF) receptor–associated periodic fever syndrome (TRAPS), and Hyper IgD syndrome (mevalonate kinase deficiency) [13]. We published that 6% of IRP patients carried a mutation in the *TNFRSF1A* gene (in most cases, the nonspecific R92Q mutation) [14]. The spectacular effect of anakinra suggests a pivotal role for the inflammasome in the pathogenesis of this condition [15].

In conclusion, the initial trigger of pericarditis may be different, while the pathway that sustains the recurrences is autoinflammatory in nature, with a pivotal role for IL-1 (Fig. 7.1).

7.5 Clinical Manifestations

The almost universal symptom of pericarditis is chest pain, worsened by lying supine and improved by leaning forward; the patients recognize it as similar to previous attacks. In addition, at least one objective finding should be present (ECG changes, pericardial rub, and pericardial effusions) [2]. Symptoms are usually milder during recurrences, particularly when appropriate treatment is begun. In patients with a more intensely inflammatory phenotype fever, strikingly elevated

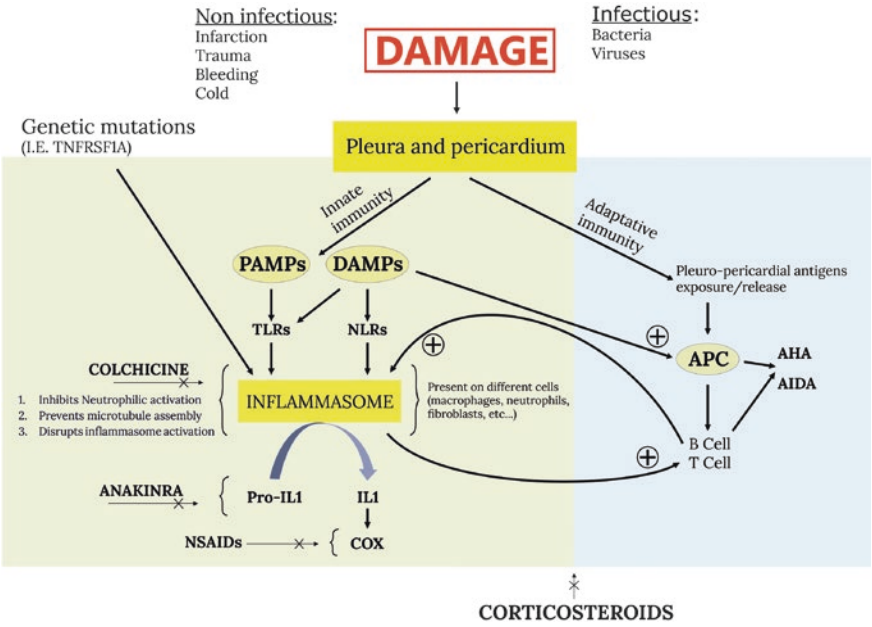

Fig. 7.1 General scheme of the supposed pathogenetic mechanisms of acute idiopathic recurrent pericarditis. *PAMP* pathogens-associated molecular patterns, *DAMPs* damage-associated molecular patterns, *TLR* toll-like receptors, *NLR* NOD-like receptors, *AHA* anti-heart antibodies, *AIDA* anti-intercalated-disk antibodies, *IL-1* interleukin-1, *NSAIDs* nonsteroidal anti-inflammatory drugs, *APC* antigen-presenting cells (from Ref. [16])

CRP, involvement of other serosal membranes (pleuropulmonary involvement in 55% of children, 36% of adults, and peritoneal involvement in 5%), and elevation of liver enzymes (8% in adult) can be recorded [17].

In the pediatric patients, the clinical picture is generally more inflammatory, with more common pleuropulmonary and systemic involvement. Accordingly, ANAs are less frequently positive in children. The autoinflammatory phenotype is clearer in children, with elevated CRP, fever, and pleural involvement [3, 18] (Table 7.1).

7.6 Laboratory Testing

There is no specific biomarker diagnostic for pericarditis. In the management of pericardial syndromes, a major controversy is the role of an extensive etiological search and admission for all patients with pericarditis or pericardial effusion [2]. The epidemiological background is essential to develop a rational cost-effective management program, and the clinician should especially identify causes that require targeted therapies. The diagnosis of "idiopathic cases" is essentially an exclusion diagnosis, supported by a typical clinical course. The ESC has proposed a diagnostic algorithm [2]. Auscultation, ECG, echocardiography, chest X-ray,

Table 7.1 Comparison of clinical features, etiologies, and outcomes in the largest published studies in pediatric (Raatikka, Imazio, Finetti) and adults (CORP2) patients with recurrent pericarditis

Feature	Raatikka [19] (*n* = 15 Children)	Imazio [18] (*n* = 110 Children)	Finetti [3] (*n* = 15 Children)	CORP2 [20] (*n* = 240 Adults)
Fever	12 (80%)	84 (76%)	8 (53%)	73 (30%)
Chest pain	15 (100%)	103 (93.6%)	13 (87%)	239 (100%)
Pericardial rub	n/a	31 (28%)	5 (33%)	82 (34%)
ECG	10/13 (77%)	49 (44%)	13 (87%)	25% [21]
Pericardial effusion	15 (100%)	86 (78%)	13 (87%)	138 (57%)
Elevated CRP	14 (93%)	102 (93%)	13 (87%)	174 (72%)
Tamponade	1 (7%)	15 (14%)	n/a	2 (1%)
No specific etiology	8 (53%)	98 (89%)	13 (87%)	198 (82%)
PPS	7 (47%)	10 (9%)	n/a	21 (9%)
ANA positivity	1 (*N* = 14) (7%)	18 (16%)	n/a	43% [7]
ASA/NSAIDs	4 (27%)	89 (81%)	13 (87%)	240 (100%)
Colchicine	4 (27%)	68 (62%)	14 (93%)	120 (50%)
Corticosteroids	11 (73%)	70 (65%)	15 (100%)	16 (7%)
Anakinra	0	12 (17.1%)	13 (87%)	0
Constriction (transient)	0 (0.0%)	3 (3%)	n/a	4 (7%)
Pleuropulmonary involvement	10 (67%)	54%	n/a	36% [17]
Liver involvement	n.a.	9 (8%)	n.a	8% [17]

CRP C-reactive protein, *ECG* electrocardiogram, *PPS* postpericardiotomy syndrome, *ANA* antinuclear antibodies, *NSAIDs* nonsteroidal anti-inflammatory drugs, *ASA* acetylsalicylic acid

routine blood tests—including markers of inflammation (i.e., CRP and/or ESR)—and myocardial lesion (troponins) are recommended in all cases of suspected pericarditis. Additional testing should be related to the suspected origin and clinical presentation. The major specific causes to be ruled out are bacterial pericarditis (especially tuberculosis), neoplastic pericarditis, and pericarditis associated with a systemic disease (generally an autoimmune disease). Each of these specific causes has a frequency of about 5% of all unselected cases of pericarditis from developed countries, while frequencies increase in moderate to large pericardial effusions [2]. Certain clinical features at presentation may be associated with an increased risk of specific etiologies (nonviral or nonidiopathic) and complications during follow-up (recurrences, tamponade, constriction), and are suggested as "high risk features" useful for the triage of pericarditis, to establish the need for a full etiological search, and admission in the single patient [2]. Factors indicated as "major" have been validated by multivariate analysis, while factors indicated as "minor" are based on experts opinion and literature review: they are essentially theoretical risk factors for complications and suggest the indication for admission and close monitoring of the evolution. Major risk factors include fever >38 °C (hazard ratio [HR], 3.56), subacute course (symptoms developing over several days or weeks; HR, 3.97), large pericardial effusion (diastolic echo-free space >20 mm in width) or cardiac

tamponade (HR, 2.15), and failure of aspirin or NSAIDs (HR, 2.50) [2]. Large effusion and tamponade (HR, 2.51) and aspirin or NSAIDs failure (HR, 5.50) also identify an increased risk of complications during follow-up (recurrences, constriction). Minor risk factors are pericarditis associated with myocarditis, immunodepression, trauma, and oral anticoagulant therapy.

For adult patients with predictors of poor prognosis, major or minor hospitalization and a full etiologic search are recommended by ESC [2]. On the contrary, when these negative predictors are absent, patients are at a low risk of specific causes and complications, and outpatient management may be considered. With a clear diagnosis of idiopathic origin and a recurrence course with complete symptom-free periods between the episodes, it is also unnecessary to repeat a new etiological search at each recurrence unless new clinical features become evident. Notably, viral serological tests are considered futile, since they have no impact on therapy and prognosis. 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 preferred for most viruses to serology, including cytomegalovirus (CMV), Epstein-Barr virus (EBV), parvovirus, adenovirus, and enteroviruses (echo and Coxsackie viruses), herpes simplex virus-1 and -2 (HSV 1 and 2) [2].

In case of a positive family history for pericarditis or periodic fever, genetic tests for monogenic syndromes may be considered [13, 14].

CRP and ESR are not specific but are important to guide the management of the disease [22]. A small study suggested that the carcinoembryonic antigen cell adhesion molecule 1 (CEACAM1) and the major histocompatibility complex (MHC) class I chain-related protein A (MICA) are possible biomarkers for IRP, but further investigations are warranted [23].

7.7 Imaging

Transthoracic echocardiography is the imaging modality of choice for the diagnosis of pericarditis [2]. It is a simple, low-cost, and noninvasive technique, easily performed at the bedside. It is safe and can be repeated without risks. It confirms the diagnosis by identifying a pericardial effusion and can demonstrate complications such as ventricular dysfunction, tamponade, constriction, etc. On the other hand, echocardiography hyperechogenicity or increased thickness of the pericardium are often limited by artifacts and are not specific.

CMR is a second-level technique that may be helpful to study pericardium and myocardium [2, 24]. On T1-weighted imaging, the normal pericardium appears like a thin hypo-intense (“dark”) curvilinear structure surrounded by hyper-intense (“bright”) epicardial and mediastinal fat. CMR may assess pericardial thickness (normal value < 4 mm) and edema. Pericardial edema appears bright on T2-weighted short-tau inverted recovery (STIR) fast spin-echo sequences. The tissue edema is not well delineated if there is a concomitant effusion, which appears as bright as the edema. Following intravenous paramagnetic gadolinium, enhancement may

demonstrate inflammation into the surrounding epicardial fat, which suggests severe inflammation. CMR is useful also in assessing myocardial edema, and fibrosis. It may also suggest evolving constrictive pericarditis. CMR is indicated also in patients in whom the presence of active pericardial inflammation is uncertain: delayed pericardial enhancement at CMR may favor continued or intensified anti-inflammatory treatment. On the other hand, if CMR does not show delayed pericardial enhancement, then tapering of medications may continue, and other diagnoses may be considered. CMR has some disadvantages, such as its limited availability and costs, and also the need of breath-holding and regular heart rhythms to get good picture quality. Contraindications include claustrophobia, pacemakers, and renal insufficiency.

CT scanning is a complementary imaging technique. It is important to evaluate presence of calcifications and anatomic features [2, 25]. The normal pericardium appears as a thin curvilinear structure surrounded by the hypodense mediastinal and epicardial fat on CT. CT can assess localized effusions, may quantify the amount of fluid and can give information about the nature of the effusion depending on attenuation values of fluid (HU). Low attenuation values (e.g., 0–20 HU) indicate a transudate, intermediate values (e.g., 20–60 HU) suggest exudative effusions, while high attenuation values (>60 HU) indicate hemorrhage. Intravenous administration of iodinated contrast may detect pericardial inflammation because of the enhancement of the inflamed pericardium after contrast injection. CT is generally considered mandatory in the preoperative work-up before pericardiectomy, to assess calcification and the anatomy of the pericardium. It is also very important to exclude important etiologies, such as neoplastic disease or tuberculosis [25].

7.8 Treatment

The treatment of patients with recurrences is not very different form the treatment of a first episode of acute pericarditis. Aspirin or NSAIDs remain the mainstay of therapy. Colchicine is recommended on top of standard anti-inflammatory therapy in order to improve remission rates and prevent recurrences. In case of incomplete response to NSAIDs and colchicine, corticosteroids may be used, but they should be added at low-to-moderate doses [2] (Tables 7.2 and 7.3).

7.9 Aspirin and Nonsteroidal Anti-inflammatory Drugs

Aspirin and NSAIDs remain the mainstay of treatment [2]. The specific drug selected is not important: the choice should be based on the physician's experience as well as on the history of efficacy and tolerability in the single patient. An NSAID that was effective in a previous attack should be the favorite drug of choice. Ibuprofen and aspirin are the most used. Indomethacin is perhaps the most powerful. Comorbidities are also important: for example, aspirin is generally not used in children, but it is the favored choice in patients with ischemic heart disease or when

Table 7.2 Nonsteroidal anti-inflammatory drugs and aspirin in the treatment of pericarditis: recommended regimens in adults

Drug	Dose	Length of Treatment	Tapering
Ibuprofen	600–800 mg every 8 h	First attack: 2–6 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 2–4 weeks and only if the patient is asymptomatic and CRP is normal), is recommended	Decrease the total daily dose by 200–400 mg every 2–4 weeks
Aspirin	500–1000 mg every 6–8 h		Decrease the total daily dose by 250–500 mg every 2–4 weeks
Indomethacin	25–50 mg every 8 h		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

The dosage ranges are based on weight, age, severity of the attack, and subjective tolerability
Adapted and reproduced by permission of Oxford University Press on behalf of the European Society of Cardiology. Please visit: https://imsva91-ctp.trendmicro.com:443/wis/clicktime/v1/query?url=www.escardio.org%2fGuidelines%2fClinical%2dPractice%2d&umid=775C782A-8734-FC05-A3F7-3C21B0DF777E&auth=1672efde352f31fd9986d5d28427f9ed7cb3c597-5f579d0d418f10a9aaa1fb328d053f7e4c4c78c4
Guidelines/Pericardial-Diseases-Guidelines-on-the-Diagnosis-and-Management-of v1.4
According to local availability of the different agents, we recommend intravenous use of NSAIDs in hospitalized symptomatic patients. Start at the lower end of dosing range and titrate upward
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
Geriatric dosing: Refer to adult dosing. Use lowest recommended dose and frequency

a patient is already on aspirin or needs antiplatelet treatment. Naproxen is an alternative. Indomethacin and other NSAIDs should be avoided in patients with coronary artery disease.

During an acute attack, a practical tip in a hospitalized patient is the administration of aspirin or NSAIDs intravenously, above all, if the patient has intensive pain, high fever with associated nausea, or vomiting. Particular attention should be paid in using the highest well-tolerated dose of each medication and to obtain a continuous anti-inflammatory coverage throughout the day. A common mistake is to use too low doses. Aspirin should be used at the dose of 1.5–4 g/day; ibuprofen at 1200–3200 mg/day; and indomethacin at 75–150 mg/day (Table 7.2). The administration

Table 7.3 Nonsteroidal anti-inflammatory drugs: recommended doses in children with pericarditis

Drug	Dose	Length of Treatment and Tapering
Ibuprofen	30–50 mg/kg/24 h divided every 8 h	First attack: 2–6 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. 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 3–4 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 two divided doses (up to 20 mg/kg/day if tolerated)	

Adapted and reproduced by permission of Oxford University Press on behalf of the European Society of Cardiology. Please visit: https://imsva91-ctp.trendmicro.com:443/wis/clicktime/v1/query?url=www.escardio.org%2fGuidelines%2fClinical%2dPractice%2d&umid=775C782A-8734-FC05-A3F7-3C21B0DF777E&auth=1672efde352f31fd9986d5d28427f9ed7cb3c597-5f579d0d418f10a9aaa1fb328d053f7e4c4c78c4
Guidelines/Pericardial-Diseases-Guidelines-on-the-Diagnosis-and-Management-of v1.4
Aspirin is generally considered contraindicated in children due to the associated risk of Reye's syndrome and hepatotoxicity
Start at the lower end of dosing range and titrate upward
CRP C-reactive protein

of NSAIDs should be well distributed during the day. For example, with regard to aspirin, ibuprofen, or indomethacin, each dose should be taken precisely in order to guarantee a full 24-h coverage [2].

7.10 Colchicine

Colchicine is recommended to be used in 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, to improve remission rates and prevent recurrences [2, 21]; similar approach is to start with 0.5 mg once daily and then, if tolerated, increase the dose to 0.5 mg twice daily or 1 mg daily, depending on compliance and tolerability. A loading dose is no more used, to avoid side effects and related early discontinuation. In children with IRP, frequently used doses are 0.5 mg/day *in children younger than* 5 years and 1–1.5 mg/day in older children [2]. Side effects are gastrointestinal (up to 10% of cases), including nausea, vomiting, diarrhea, and abdominal pain, usually being a common cause of drug withdrawal; generally mild, they may resolve with dose reduction. The duration of therapy is at least 6 months, but, if recurrences are frequent and colchicine is well tolerated, the duration can reach some years. At this point, discontinuation is discussed with the patient, and we prefer to taper it slowly.

7.11 Corticosteroids

Only after the use of high dosages of NSAIDs, corticosteroids may be added to aspirin/NSAIDs and colchicine as a triple therapy in cases of incomplete clinical control of the disease, particularly in adults, 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 many inflammatory mediators.

Although corticosteroids provide rapid control of symptoms, they favor chronicity, more recurrences, and side effects [2, 17, 18, 20, 24]. If corticosteroids are used, their tapering should be particularly slow. A critical threshold for recurrences is a 10–15 mg/day dose of prednisone or equivalent. At this threshold, very slow decrements as small as 1.0–2.5 mg at intervals of 2–6 weeks are useful. In cases of recurrence, every effort should be made not to increase the dose or to reinstate corticosteroids [2].

Corticosteroids should be used only in selected patients with specific indications (i.e., impending cardiac tamponade, pregnancy, systemic inflammatory diseases, some patients with postpericardiotomy syndromes), intolerance or resistance to standard therapy, and NSAID contraindications (renal insufficiency, true allergy, high risk of bleeding) [2]. Every decrease in corticosteroid dose should be done only if the patient is asymptomatic and CRP is normal. Calcium intake (supplement plus oral intake) of 1200–1500 mg/day and vitamin D supplementation of 800–1000 IU/day should be offered to all adult patients receiving glucocorticoids. Moreover, bisphosphonates are recommended to prevent bone loss in all men $\geq$ 50 years and postmenopausal women in whom long-term treatment with glucocorticoids is initiated at a dose $\geq$ 5.0–7.5 mg/day of prednisone or equivalent.

The increased risk of recurrences in patients treated with corticosteroids may well be due to too rapid tapering, not driven by symptoms and CRP values. Long-term corticosteroid use is particularly worrisome in pediatric patients due to their multiple side-effects, including growth impairment.

7.12 Tapering

After obtaining a complete response, tapering should be done with a single class of drug at a time, and finally, colchicine is gradually discontinued (over several months in the most difficult cases). Recurrences are possible after discontinuation of each drug. Each tapering should be attempted only if symptoms are absent and CRP is normal. For these reasons, the length of therapy may extend for months or even years in the more difficult cases.

7.13 Immunotherapy and IL-1 Inhibition

Immunotherapy is an alternative approach to treat refractory IRP [2]. Three drugs have been proposed: azathioprine, intravenous immunoglobulins (IVIg), and anakinra.

Azathioprine has been used in case reports or case series of adults and one retrospective cohort study [26].

IVIgs have been used in two small case series and one retrospective analysis describing only 14 cases [2]. IVIgs can be used as a corticosteroid-sparing agents and have a rapid onset of action; however, they are rarely used, probably due to the high cost and lack of good evidence.

Anakinra is a recombinant IL-1 receptor antagonist; it inhibits the action of IL-1. The IL-1 intracellular signaling pathway is involved in the prostaglandin release by macrophages and in chemotaxis of monocytes, lymphocytes, and polymorphonuclear leukocytes, in the activation of T cells, and in the stimulation of metalloproteinases. Anakinra was initially registered for the treatment of rheumatoid arthritis, but it has found its niche in the treatment of several rare autoinflammatory diseases. Its spectacular effect in IRP was first recognized in the pediatric population [3, 18], and this was a proof of concept. Other case reports, cohort studies, one retrospective analysis, and a meta-analysis confirmed these findings. Finally, a double-blind randomized controlled trial (AIRTRIP-The Anakinra-Treatment of Recurrent Idiopathic Pericarditis) formally demonstrated the efficacy of anakinra in 21 patients with corticosteroid-dependent and colchicine-resistant recurrent pericarditis with elevated CRP [4]. Anakinra obtained quick symptom relief in a few days and allowed steroid discontinuation in all patients within 6 weeks. It was administered as a once daily subcutaneous injection at the dose of 100 mg in adults (1–2 mg/kg/day in children) for 6 months [4]. Recurrences can occur if tapering is too rapid. Tapering regimes are not established, and it is very difficult to propose a universal tapering regimen (as it would very difficult to propose a similar tapering regimen for corticosteroids for instance). A possible scheme might be to withdraw a dose every month after a full control of the disease has been reached: for example, first step, 100 mg/day, every day for 6 months; second step, in the 7th month, 100 mg/day, six times per week; third step, 100 mg/day, five times per week for 1 month, and so on until the seventh step, 100 mg once per week, in the 14th month. A critical point for recurrence might be at the dose of two doses weekly. A similar approach would be the following: when the patient reaches the three dose/weekly regimen, the following tapering may be done not considering the week but considering the interval between two consecutive doses, for instance, one dose every third day, then every fourth day, and so on.

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 such as canakinumab in IRP [27].

7.14 Outcome and Prognosis

Severe complications are rare in IRP [2]. Cardiac tamponade is uncommon and usually occurs at the beginning of the disease. A small risk to evolve in constrictive pericarditis exists after the first episode of acute pericarditis (less than 1%) [28], but on the other hand, constrictive pericarditis has never been reported in IRP, in spite of numerous recurrences [17, 29]. Thus, it is important to reassure patients about their prognosis, explaining the likely course and the nature of the disease. Drug treatment should take into account this favorable outcome to avoid iatrogenic damages, particularly due to corticosteroids, particularly in the pediatric patients. However, the quality of life can be severely impaired due to repeated recurrences, frequent hospitalizations, and corticosteroid dependence [2]. IRP may last for years if not properly treated. IL-1-inhibitors have proved to be quick and highly efficient, also in refractory cases, and their role is becoming more prominent. In our experience, most patients continue treatment with anakinra 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].

References

1. Maestroni S, Di Corato PR, Cumetti D, et al. Recurrent percarditis; autoimmune or autoinflammatory? Autoimmun Rev. 2012;12:60–5.
2. Adler Y, Charron P, Imazio M, et al. 2015 ESC guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) endorsed by: the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2015;36:2921–64.
3. Finetti M, Insalaco A, Cantarini L, Meini A, Breda L, Alessio M, D'Alessandro M, Picco P, Martini A, Gattorno M. Long-term efficacy of interleukin-1 receptor antagonist (anakinra) in corticosteroid-dependent and colchicine-resistant recurrent pericarditis. J Pediatr. 2014;164:1425–31.
4. Brucato A, Imazio M, Gattorno M, et al. Effect of anakinra on recurrent pericarditis among patients with colchicine resistance and corticosteroid dependence—The AIRTRIP Randomized Clinical Trial. JAMA. 2016;316:1906–12.
5. Kobberoe Sogard K, Farkas Kormendine D, Ehrenstein V, Bhaskaran K, Botker HE, Sorenson HT. Pericarditis as a marker of occult cancer and a prognostic factor for cancer mortality. Circulation. 2017;136(11):996–1006. (Epub ahead of print).
6. Brucato A, Brambilla G. Recurrent idiopathic pericarditis: familial occurrence. Int J Cardiol. 2005;102:529.
7. Imazio M, Brucato A, Doria A, et al. Antinuclear antibodies in recurrent idiopathic pericarditis: prevalence and clinical significance. Int J Cardiol. 2009;136:289–93.
8. Caforio AL, Brucato A, Doria A, et al. Anti-heart and anti-intercalated diskautoantibodies: evidence for autoimmunity in idiopathic recurrent acute pericarditis. Heart. 2010;96:779–84.
9. Lazaros G, Karavidas A, Spyropoulou M, et al. The role of the immunogenetic background in the development and recurrence of acute idiopathic pericarditis. Cardiology. 2011;118:55e62.
10. Hoffman M, Fried M, Jabareen F, et al. Anti-heart antibodies in postpericardiotomy syndrome: cause or epiphenomenon? A prospective, longitudinal pilot study. Autoimmunity. 2002;35:241–5.
11. Imazio M. Pericardial involvement in systemic inflammatory diseases. Heart. 2011;97:1882–92.

12. Picco P, Brisca G, Martini A, et al. Successful treatment of idiopathic recurrent pericarditis in children with interleukin-1β receptor antagonist (anakinra). Arthritis Rheum. 2009;60:264–8.
13. Rigante D, Cantarini L, Imazio M, et al. Autoinflammatory diseases and cardiovascular manifestations. Ann Med. 2011;43:341–6.
14. Cantarini L, Lucherini OM, Brucato A, et al. Clues to detect tumor necrosis factor receptor-associated periodic syndrome (TRAPS) among patients with idiopathic recurrent acute pericarditis: results of a multicentre study. Clin Res Cardiol. 2012;101:525–31.
15. Xu B, Harb SC, Cremer PC. New insights into pericarditis: mechanisms of injury and therapeutic targets. Curr Cardiol Rep. 2017;19:60.
16. Brucato A, Emmi G, Cantarini L, Di Lenarda A, Gattorno M, Lopalco G, Marcolongo R, Imazio M, Martini A, Prisco D. Management of idiopathic recurrent pericarditis in adults and in children: a role for IL-1 receptor antagonism. Intern Emerg Med. 2018;13(4):475–89. https://doi.org/10.1007/s11739-018-1842-x.
17. Brucato A, Brambilla G, Moreo A, et al. Long-term outcomes in difficult-to-treat patients with recurrent pericarditis. Am J Cardiol. 2006;98:267–71.
18. Imazio M, Brucato A, Pluymaekers N, et al. Recurrent pericarditis in children and adolescents: a multicentre cohort study. J Cardiovasc Med (Hagerstown). 2016;17:707–12.
19. Raatikka M, Pelkonem PM, Karjalainen J, et al. Recurrent pericariditis in children and adolescents. J Am Coll Cardiol. 2003;42:759–64.
20. Imazio M, Belli R, Brucato A, et al. Efficacy and safety of colchicine for treatment of multiple recurrences of pericarditis (CORP-2): a multicentre, double-blind, placebo-controlled, randomized trial. Lancet. 2014;383:2232–7.
21. Imazio M, Brucato A, Cemin R, et al. A randomized trial of colchicine for acute pericarditis. N Engl J Med. 2013;369:1522–8.
22. Imazio M, Brucato A, Maestroni S, et al. Prevalence of C-reactive protein elevation and time course of normalization in acute pericarditis: implications for the diagnosis, therapy, and prognosis of pericarditis. Circulation. 2011;123:1092–7.
23. Markel G, Imazio M, Koren-Morag N, et al. CEACAM1 and MICA as novel serum biomarkers in patients with acute and recurrent pericarditis. Oncotarget. 2016;7:17885–95.
24. Cremer PC, Kumar A, Kontzias A, et al. Complicated pericarditis: understanding risk factors and pathophysiology to inform imaging and treatment. J Am Coll Cardiol. 2016;68:2311–28.
25. Maggiolini S, De Carlini CC, Ferri LA, et al. The role of early contrast-enhanced chest computed tomography in the aetiological diagnosis of patients presenting with cardiac tamponade or large pericardial effusion. Eur Heart J Cardiovasc Imaging. 2016;17:421–8.
26. Vianello F, Cinetto F, Cavraro M, et al. Azathioprine in isolated recurrent pericarditis; a single centre experience. Int J Cardiol. 2011;147:477–8.
27. Kougkas N, Fanouriakis A, Papalopoulos I, Bertsias G, Avgoustidis N, Repa A, Sidiropoulos P. Canakinumab for recurrent rheumatic disease associated-pericarditis: a case series with long-term follow-up. Rheumatology (Oxford). 2018;57(8):1494–5. https://doi.org/10.1093/rheumatology/key077.
28. Imazio M, Brucato A, Maestroni S, et al. Risk of constrictive pericarditis after acute pericarditis. Circulation. 2011;124:1270–5.
29. Imazio M, Brucato A, Adler Y, et al. Prognosis of idiopathic recurrent pericarditisas determined from previously published reports. Am J Cardiol. 2007;100:1026–8.